Syntheses and transformations of alicyclic β-amino acid derivatives

PhD Thesis

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2005

To my beloved family, who have always stood by me

If there is one way better than another, it is the way of nature.

(Aristotle)

CONTENTS

ABBREVIATIONS AND SYMBOLS

ACE	Angiotenzin I Converting Enzime
ACHC	2-aminocyclohexane-1-carboxylic acid
ACPC	2-aminocyclopentane-1-carboxylic acid
AIBN	azoisobutyronitrile
BINOL	1,1'-binaphthyl-2,2'-diol
Boc	*tert*-butyloxycarbonyl
Bom	benzyloxymethyl
Bu_3SnH	tributyltin hydride
CAL-B	lipase from *Candida Antarctica* fraction B
CDI	1,1'-carbonyl diimidazole
CSI	chlorosulfonyl isocyanate
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIFFNOE	NOE Difference Spectroscopy
DHAA	(+)-*trans*-2,3-dihydro-3-hydroxyanthranylic acid
DMF	*N,N*-dimethylformamide
DMPU	*N,N'*-dimethyl propylene urea
DPPA	diphenylphosphorylazide
ee	enantiomeric excess
Fmoc	9-fluorenylmethoxycarbonyl
IPC_2BH	diisopinocamphenyl borane
KHMDS	potassium hexamethyldisilylazide dimer
LiHMDS	lithium hexamethyldisilylazide
MCPBA	*m*-chloroperbenzoic acid
Ms	mesyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	two-dimensional nuclear Overhauser spectroscopy
ORTEP	oak ridge thermal ellipsoid plot program
PLE	pig liver esterase
r	correlation coefficient
T	temperature
TBHP	*tert*-butyl-hydroperoxyde
TBSCl	tributylsilyl chloride
TFA	trifluoroacetic acid
THF	tetrahydrofurane
Ts	toluenesulfonyl
δ	chemical shift
σ^+	Hammett-Brown parameter
Z	benzyloxycarbonyl

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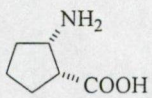
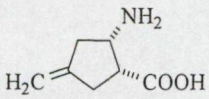
1. INTRODUCTION AND AIMS

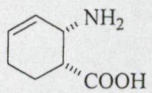
Alicyclic β-amino acids play important roles in chemistry and biology. In 1989, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin)[1,2] an antifungal antibiotic, was isolated from *Bacillus cereus*[1] and *Streptomyces setonii;*[3] it is also a component of the antibiotic amipurimycin.[4] An antifungal antibiotic BAY y 9379 and the hydrochloride salt of (1*S*,6*R*)-6-amino-3,4-dimethylcyclohex-3-ene-1-carboxylic acid, which were originally designed at Bayer AG as pyridoxal phosphate suicide inhibitors, turned out to have activity against *Candida albicans* as well.[5] (1*R*,2*S*)-2-Amino-4-methylenecyclopentanecarboxylic acid (BAY 10-8888) is currently under investigation in phase II clinical trials as a novel antifungal for the treatment of yeast infections (Scheme 1).



cispentacin



BAY 10-8888



BAY y 9379

Scheme 1

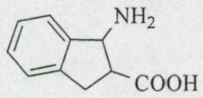
2-Aminocycloalkanecarboxylic acids, important non-proteinogenic β-amino acids, have many applications in the syntheses of natural products,[6] biologically active compounds,[7] heterocycles[8] and peptidomimetics. The synthesis, stereochemistry and transformations of cyclopentane-, cyclohexane-, cycloheptane- and cyclooctane-fused 1,3-oxazines, 1,3-thiazines and pyrimidines have been reviewed. Many of these syntheses started from cyclic 2-aminocycloalkanecarboxylic acid or their derivatives and have already been reviewed.[8,9]

Particularly since their oligomers were demonstrated to fold into stable helical conformations, β-amino acids have been the subject of much synthetic effort in recent years.[10-12]

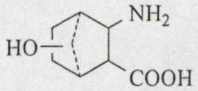
In spite of the publication of several different methods for the preparation of racemic and enantiopure cyclic hydroxy-β-amino acid derivatives in the past two decades, these methods have not yet been reviewed. The aim of the literature part of my thesis is to summarize the results in this intensively developing field of research.

My PhD work was focused on the syntheses of new β-amino acids: the synthesis of all four enantiomers of 1-aminoindane-2-carboxylic acid, a new cispentacin benzologue [III], and the preparation of *cis*- and *trans*-2-amino-4- and -5-

hydroxycyclohexane-carboxylic acids [VI] and 3-amino-5- and -6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acids [VII] by stereoselective and regioselective functionalizations of *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acid and *diendo*-3-aminobicyclo-[2.2.1]hept-5-ene-2-carboxylic acid derivatives via 1,3-oxazine or γ-lactone intermediates (Scheme 2).



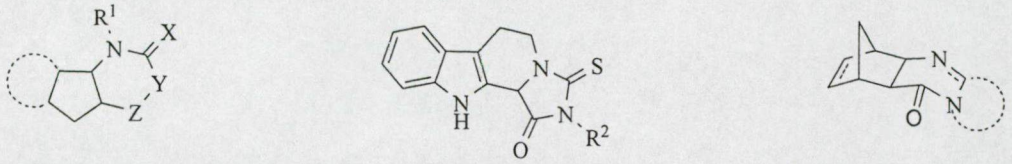
cis, trans



cis, trans. diendo

Scheme 2

A further aim was a comparative study of the ring-closure reactions of *cis*- and *trans*-2-amino-1-cyclopentanecarboxylic acid derivatives [II], *cis*- and *trans*-1-aminoindane-2-carboxylic acid derivatives [V] and *N*-ureido- and thioureido-1,2,3,4-tetrahydro-*β*-carboline-1-carboxylic acid esters [IV], and the ring-enlargement of norbornane- and norbornene-fused azetidinones [I] (Scheme 3).



X = S, NEt; Y = O, S, Nalk; Z = CO, CH_2; R^1 = H, Bz ; R^2 = Me, Et, Pr, *n*-Bu, Ph, *p*-tolyl, *p*-Cl-C_6H_4, *p*-OMe-C_6H_4

Scheme 3

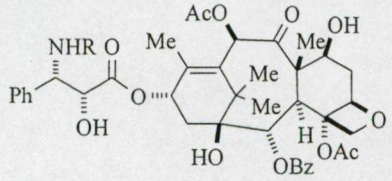
All compounds investigated in the Results part of my thesis were racemates, except for **97-104** [III]. The Schemes depict only one of the enantiomers, except in Scheme 22, where optically active compounds are discussed and the absolute configurations are shown.

The publications on which the thesis is based (listed on page 5) are given in square brackets, while other references are given as superscripts.

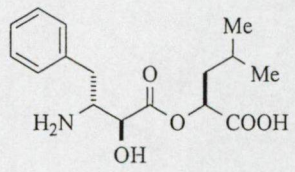
2. LITERATURE

2.1. Importance of hydroxylated β-amino acids

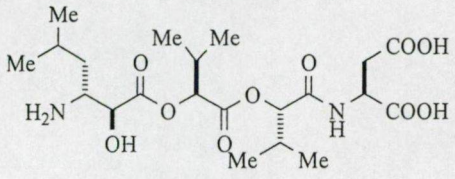
Hydroxy-β-amino acids constitute an important class of amino acids, because of their occurrence in many biologically relevant compounds.[13] Paclitaxel (Taxol®) and docetaxel (Taxotere®) are amongst the most effective chemotherapeutic agents for the clinical treatment of ovarian and breast cancers today.[14-17] Representative examples are the aminopeptidase inhibitors bestatin[18,19] and amastatin[20] and the ACE inhibitor microginin,[21,22,] which contain aliphatic derivatives (Scheme 4). Some cyclic derivatives have antibiotic (oryzoxymycin)[23-26] or antifungal activities,[27,28] or are building blocks for pharmaceutically important natural substances such as fortamine,[6, 29] chryscandin,[30] pentopyraneamine,[31] gougerotin,[32] and blasticidin.[33]



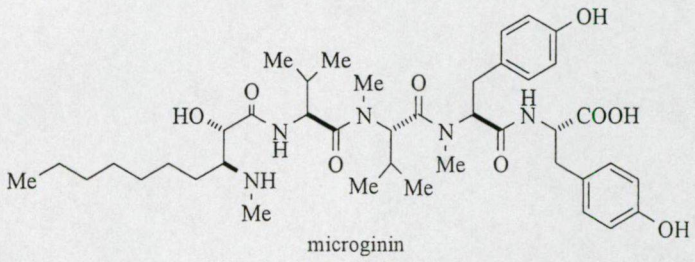
R = Bz; Taxol®
R = CO_2But; Taxotere®



bestatin



amastatin



microginin

Scheme 4

Hydroxylated β-amino acids function as precursors for the synthesis of β-lactams[34,35] and heterocyclic compounds.[36]

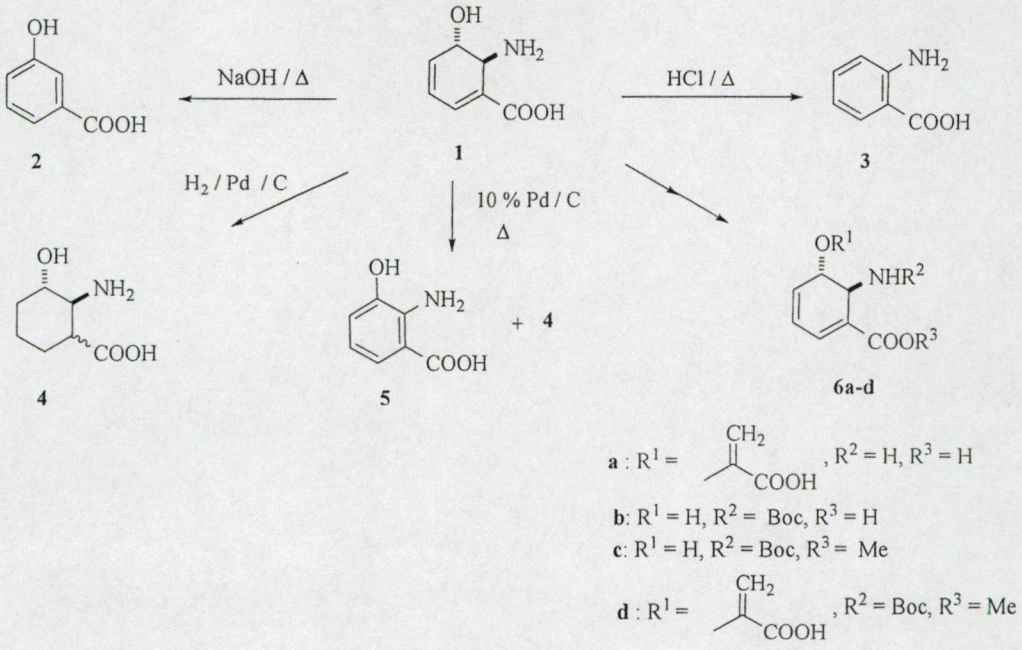
It has been demonstrated that oligomers composed of β-amino acids can fold stable secondary structures similar to those of α-peptides, helices, sheets and turns.[10,37] It was most intriguing discovery that only 6 β-amino acid residues are enough for the formation of a stable helix,[38,39] whereas an α-amino acid oligomer normally requires 15-20 residues. The formation of the helical structure of β-peptides was strongly influenced by the nature and stereochemistry of the amino acid side-chains at both the α- and β-positions. In 2001, Tromp *et al.* prepared α-hydroxylated β-oligopeptides in solid-phase syntheses. NMR studies on the resulting α-hydroxylated β-hexapeptide indicated that in

pyridine no helical structure was formed.[40] In contrast, in 2002, Woll *et al.* reported that oligomers composed of 3-methoxy- or 3-phenoxy-substituted ACPC residues maintain the 12-helical conformation displayed by the non-substituted analogues.[41] These facts reveal that the presence of the unprotected α-hydroxy group exerts a great influence on the formation of the secondary structure.

2.2. Syntheses of hydroxylated alicyclic β-amino acids

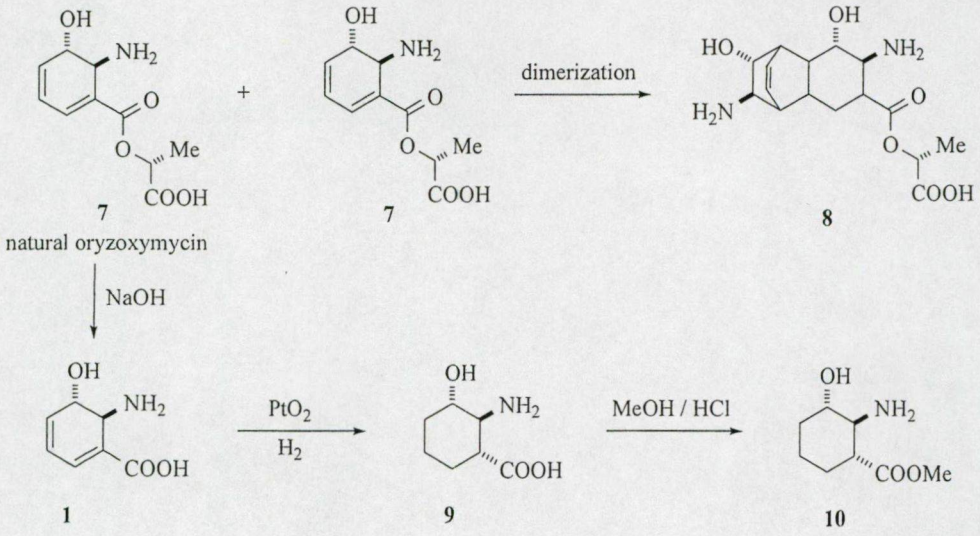
2.2.1. Natural hydroxylated alicyclic β-amino acids

In 1961, McCormick *et al.* isolated a new amino acid from the fermented mash of a *Streptomyces aureofaciens* mutant.[42] This substance was characterized as (+)-*trans*-2,3-dihydro-3-hydroxyanthranilic acid (**1**, DHAA) via its elemental analysis, its ultraviolet and infrared absorption spectra, and its chemical transformations. The conversion of DHAA to anthranilic acid (**3**) under vigorous acidic conditions and to *m*-hydroxybenzoic acid (**2**) under vigorous alkaline conditions confirmed the structure. Catalytic hydrogenation of DHAA led to 3-hydroxyanthranilic acid (**5**) and hexahydro-3-hydroxyanthranilic acid (**4**) (Scheme 5). At that time, no conclusive evidence was found for the configurational relationship of the amino and hydroxy groups, but the vigorous conditions required for the acidic dehydration of DHAA to anthranilic acid strongly suggested that these groups are *trans* to each other. No evidence was obtained either for the configuration of C-1 in **4** relative to the other two asymmetric centres. However, the reduction was shown to be stereoselective by the isolation of **4** as a single substance in high yield.[43] The complete stereochemistry of DHAA was proved by Teng and Ganem, who established the absolute configuration of DHAA as (2*S*,3*S*) and prepared its *N*-Boc and ester derivatives (**6a-d**).[44] Policastro *et al.* prepared the (5*S*,6*S*)-6-amino-5-[(1-carboxyethenyl)oxy]-1,3-cyclohexadiene-1-carboxylic acid derivative (**6a**) and described its biochemical transformation to anthranilic acid (**2**) with pure *S. marcescens* AS I enzyme.[45]



Scheme 5

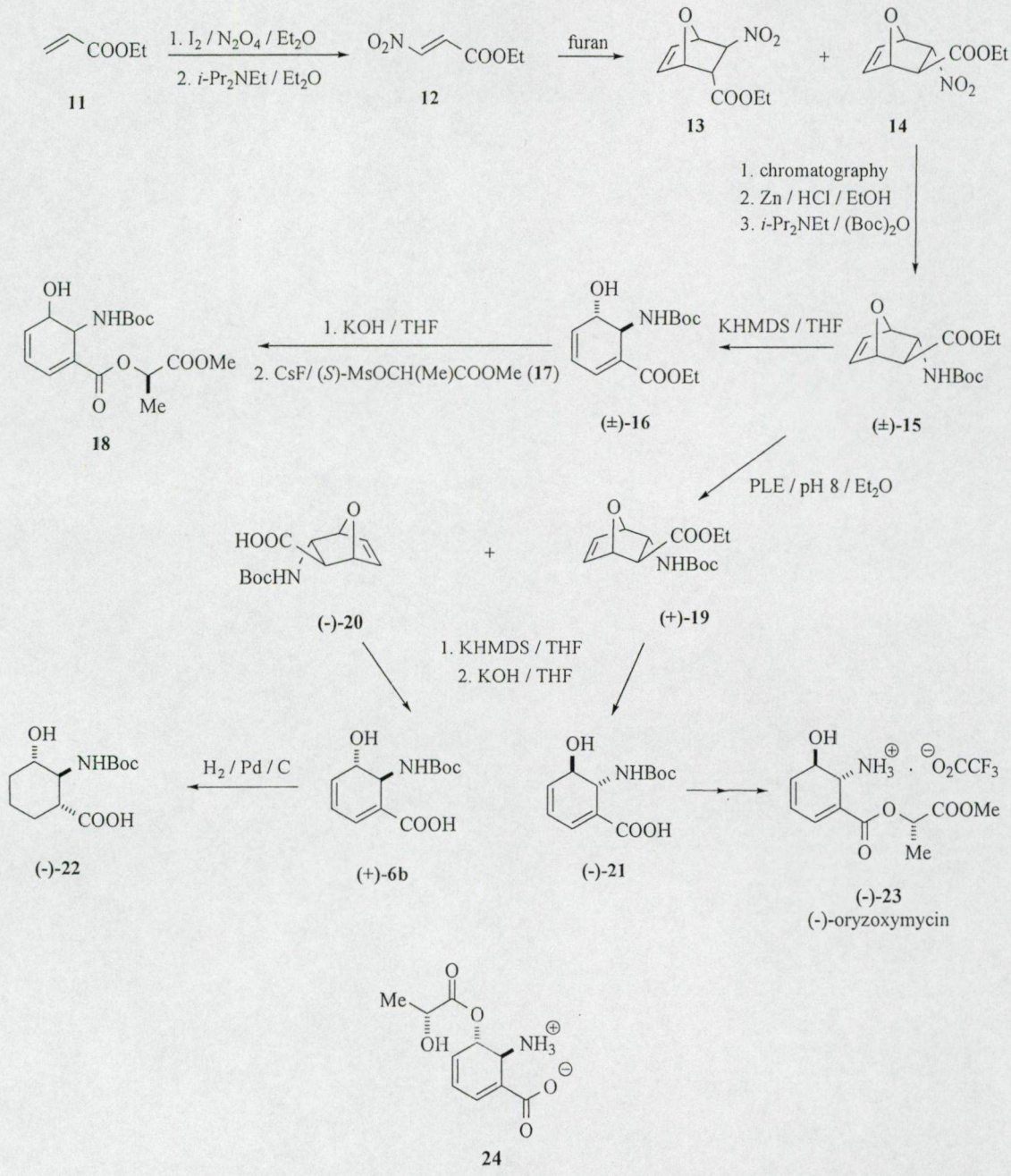
From a soil sample of a *Streptomyces* strain Hashimoto *et al.* isolated a novel metabolite, oryzoxymycin **7**, which exhibited moderate *in vitro* activity against *Xanthomonas oryzae*.[23,24] Oryzoxymycin was readily converted to an inactive crystalline dimerization product **8**. Hydrolysis of oryzoxymycin gave *R*-lactic acid and (2*S*,3*S*)-6-amino-*trans*-5-hydroxy-1,3-cyclohexadiene-1-carboxylic acid (**1**), which was converted through atmospheric catalytic hydrogenation on Adams platinum oxide to the hexahydro-hydroxyamino acid **9** (Scheme 6). The melting points and the optical rotation data for **9** and **4** were identical, and the two compounds were therefore presumably the same. Esterification of **9** with hydrogen chloride in methanol at room temperature afforded ester derivative **10**.[25] The absolute configurations of **7** and **9** were determined by NMR spectroscopy and the copper complex (TACu) method. From these data, the absolute structure of **7** must be (2*R*,5*S*,6*S*)-2-[6-amino-5-hydroxy-1,3-cyclohexadiene-1-carbonyloxy]propanoic acid, while the absolute configuration of **9** is (1*R*,2*S*,3*S*).



Scheme 6

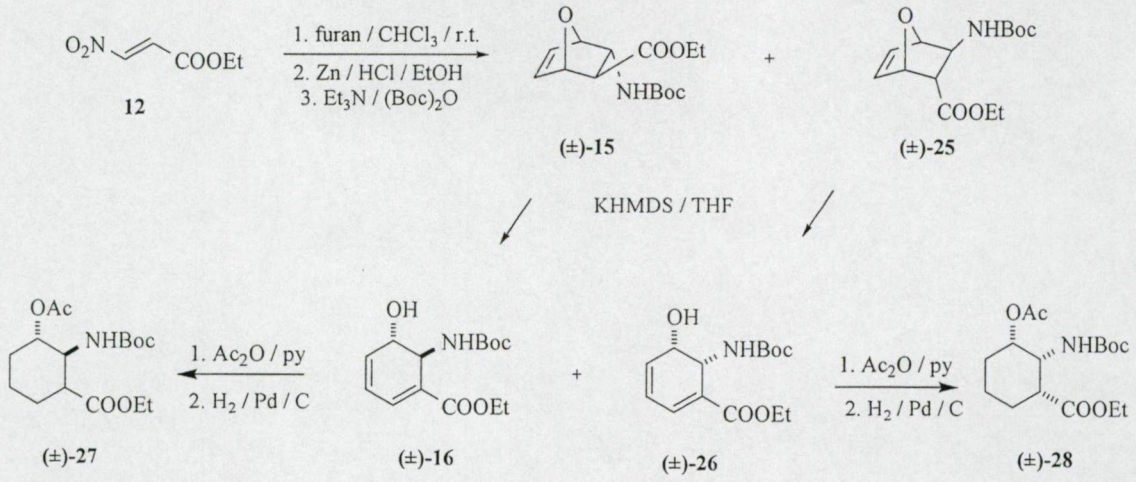
In 2003, Steel *et al.* reported an asymmetric synthesis of putative (-)-oryzoxymycin (**23**) and an asymmetric synthesis of the dihydroxyanthranilate core.[26] In the first step, the Diels-Alder reaction of furan with nitroacrylate **12** occurred rapidly to give a mixture of cycloadducts favouring the expected *endo* nitro isomers **14** (4:1). Subsequent selective conversion to the anthranilate ester **16** was achieved through the protected amino ester **15**. Hydrolysis of **16** and its reaction with mesylate **17** gave the desired lactate product **18** as a mixture of two diastereomers. Separation of the diastereomers proved impossible; accordingly, the authors developed an enantioselective preparation of ester **15.** The PLE-catalysed selective hydrolysis of bicyclic ester **15** gave the enantiomer ester **19** and acid **20**. With the chiral esters available, the synthesis was repeated starting from enantiomer **19**, and putative (-)-oryzoxymycin **23** was obtained.

The optical rotations of the natural **7** and synthetic **23** oryzoxymycins were different (**23**: $[\alpha]_D^{21}$ = -199 (c = 1, H_2O); **7**: lit.[24] $[\alpha]_D^{21}$ = +349 (c = 1, H_2O)) and in the IR spectrum revealed significant differences both in the carbonyl region and in the characteristic bands of the fingerprint region. The authors suggested that the correct structure of oryzoxymycin may be the isomeric C-5 lactate ester **24** and promised to prepare this compound to verify this hypothesis (Scheme 7).[26]



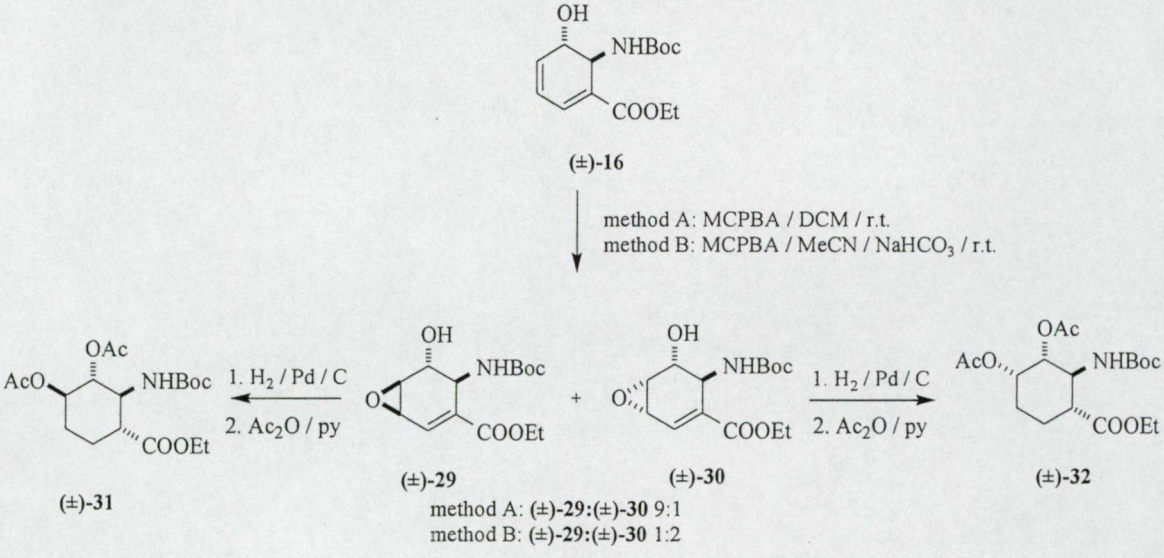
Scheme 7

In 2004, the same research team reported the synthesis of 3-hydroxy and 3,4-dihydroxy derivatives of ACHC.[46] Under Diels-Alder conditions two isomers were isolated, which were easily separated by column chromatography. Nitro group reduction and protection of the resultant amines gave carbamates **15** and **25**. Subsequent *β*-elimination of the oxygen bridge of carbamates **15** and **25** gave dihydroanthranilates **16** and **26**. Acylation and reduction of these acetates afforded 3-hydroxy-ACHC derivatives: *trans-trans* **27** from **16** and *cis-cis* **28** from **26** (Scheme 8). The relative stereochemistry of carbamate **15** was confirmed by X-ray crystallography, and the structures of the other derivatives were confirmed by 2D NMR spectroscopy.



Scheme 8

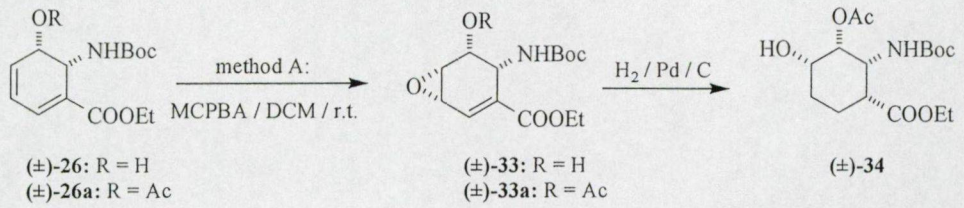
The preparation of 3,4-dihydroxy derivatives of ACHC was possible via reductive opening of epoxide intermediates derived from cyclohexadienes **16** and **26** (Scheme 9). Treatment of **16** with *m*-chloroperbenzoic acid in dichloromethane gave a separable mixture of epoxides **29**:**30** = 9:1 (method A). Repetition of the epoxidation of **16** in acetonitrile instead of dichloromethane preserved the stereoselectivity and gave a 2:1 mixture of the isomers favouring the *cis* epoxy alcohol **30** (method B). Reductive opening of the corresponding epoxides in the presence of Pd-C in hydrogen atmosphere gave the *all-trans* **31** and *trans-trans-cis* **32** dihydroxy ACHC derivatives as the only isomers. The configurations of **31** and **32** were confirmed by NOESY experiments.



Scheme 9

Epoxidation of **26** by method A afforded epoxide **33** as the only product in high yield. All attempts with the use of polar solvents or starting from acetate **26a** failed to give the *trans* epoxy alcohol. Reduction of epoxide **33a** afforded the *all-cis* isomer **34**

(Scheme 10). It is pertinent to note that the combination involving the above-mentioned PLE-mediated kinetic resolution method[26] is applicable for the preparation of the enantiomers of derivatives **28**, **31**, **32** and **34**.



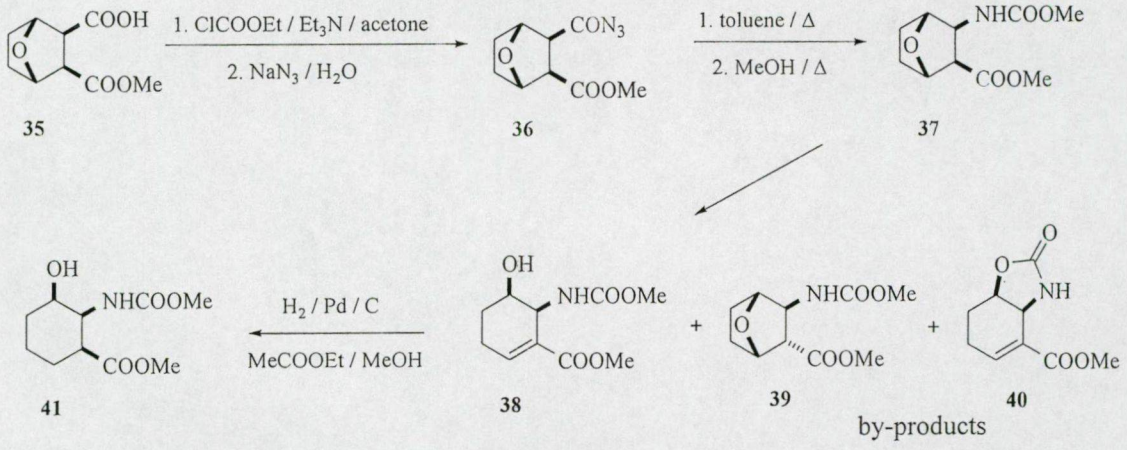
(±)-26: R = H
(±)-26a: R = Ac

(±)-33: R = H
(±)-33a: R = Ac

(±)-34

Scheme 10

Couche *et al.* reported on the synthesis of enantiomerically enriched 2-amino-3-hydroxycyclohexanecarboxylic acid derivatives, starting with an asymmetrization step.[47] Enantiomerically pure (*ee* > 98%) mono ester **35,** obtained by PLE-catalysed hydrolysis of the corresponding *meso* diester**,** was activated by mixed anhydride and treated with sodium azide to afford the desired acyl azide **36**. Subsequent Curtius rearrangement and trapping of the intermediate isocyanate with methanol gave the bicyclic amino compound **37**. Basic ring opening of the bicycle **37** proved fairly sensitive to the reaction conditions, due to side-reactions involving either epimerization of the carbomethoxy group (**37**→**39**) or an intramolecular reaction leading from **37** to the oxazolidinone **40**. Under the best conditions (LiHMDS 2.2 equivalents, THF, -10 °C) the reaction proceeded without any by-product formation but the conversion was incomplete and the cyclohexene derivative **38** was formed in low yield (41%). Catalytic hydrogenation of the double bond of **38** resulted in the single diastereomer of **41** (Scheme 11).



35 **36** **37**

41 **38** **39** **40**

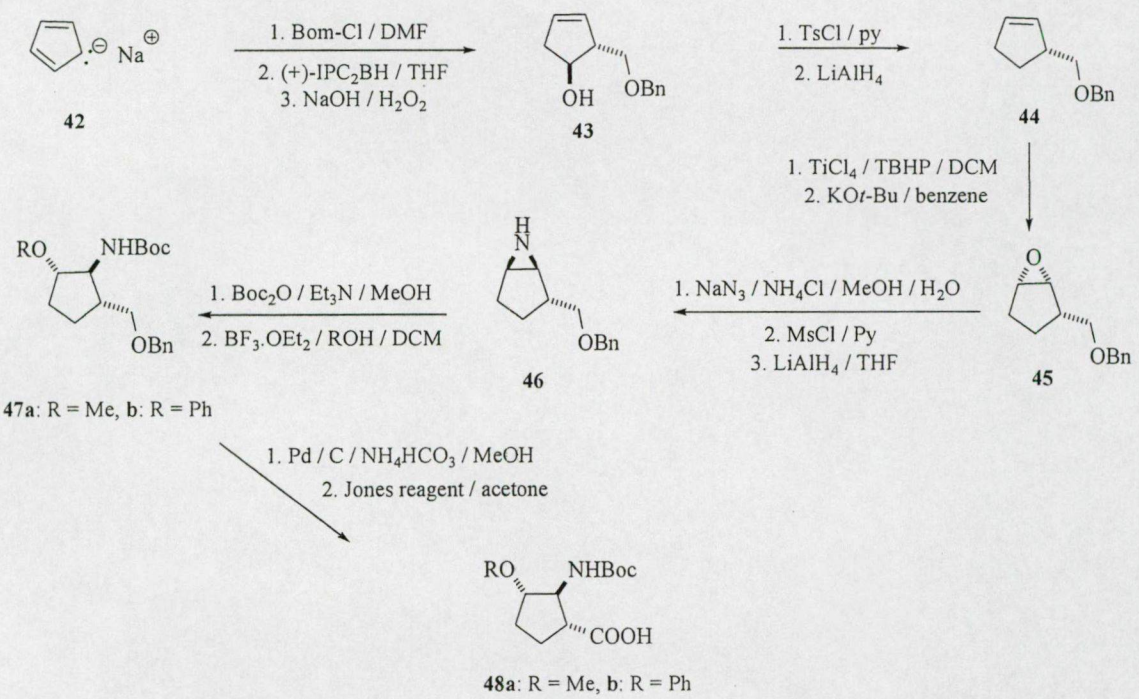
by-products

Scheme 11

2.2.2. Synthetic alicyclic hydroxy β-amino acids

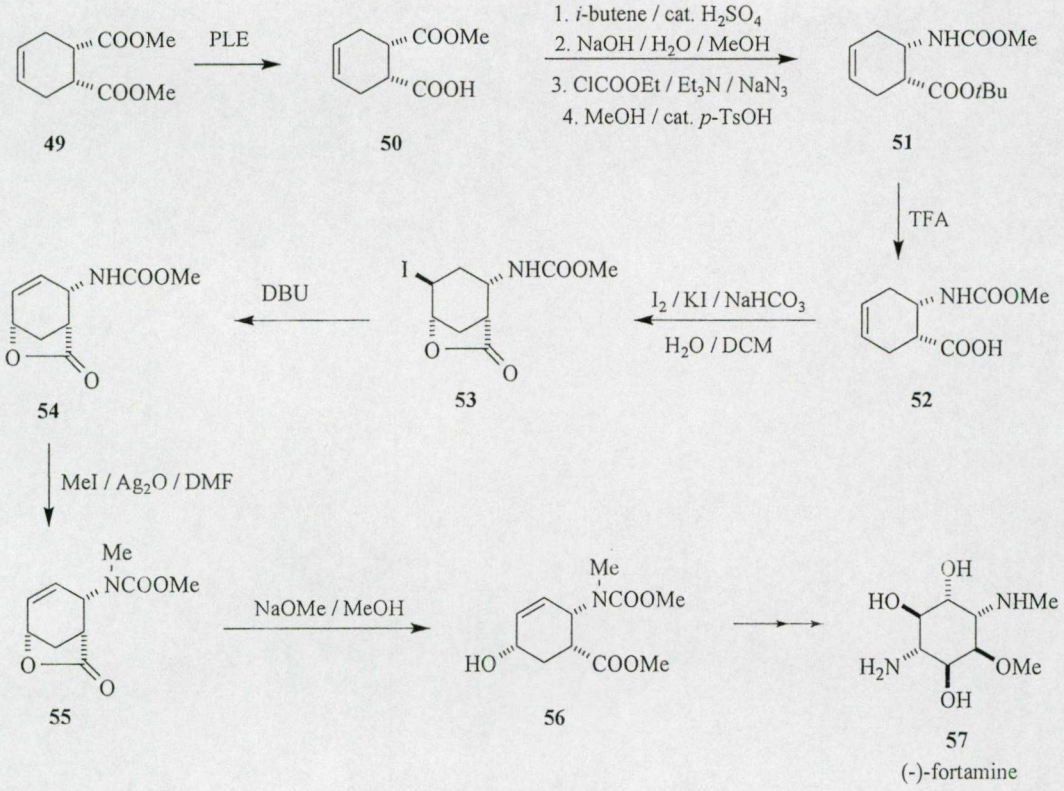
2.2.2.1. By functionalization of ring double bonds

Gellman *et al.* reported on the stereoselective synthesis of 3-substituted 2-aminocyclopentanecarboxylic acids and their incorporation into short 12-helical *β*-peptides that fold in water.[41] The phenoxy and methoxy-substituted monomers (**48a,b**) were prepared enantioselectively, starting with the alkylation of sodium cyclopentadiene (Scheme 12). The resulting diene **42** was then converted to the *cis*-epoxide **45**. Epoxide ring opening with sodium azide, followed by alcohol activation with mesyl chloride, yielded a 2:3 regioisomeric mixture of azido-mesylates, which was converted to **46** by azide reduction and concomitant ring-closing mesylate displacement. The ring-opened **47a** and **47b** were converted to their respective *N*-Boc-*β*-amino acids **48a** and **48b** by removal of the benzyl protecting group, followed by oxidation. A protecting group change from Boc to Fmoc afforded *β*-amino acid derivates suitable for solid-phase synthesis. Their circular dichroism signatures and NMR analysis data demonstrated that the hexamers composed of the 3-substituted ACPC residues (**48a,b**) maintained the 12-helical conformation previously shown for the non-substituted analogue. 3-Substituted ACPC residues allow the arrangement of specific functional groups in a geometrically defined fashion, which should facilitate the design of *β*-peptides for biological applications.[48,49]



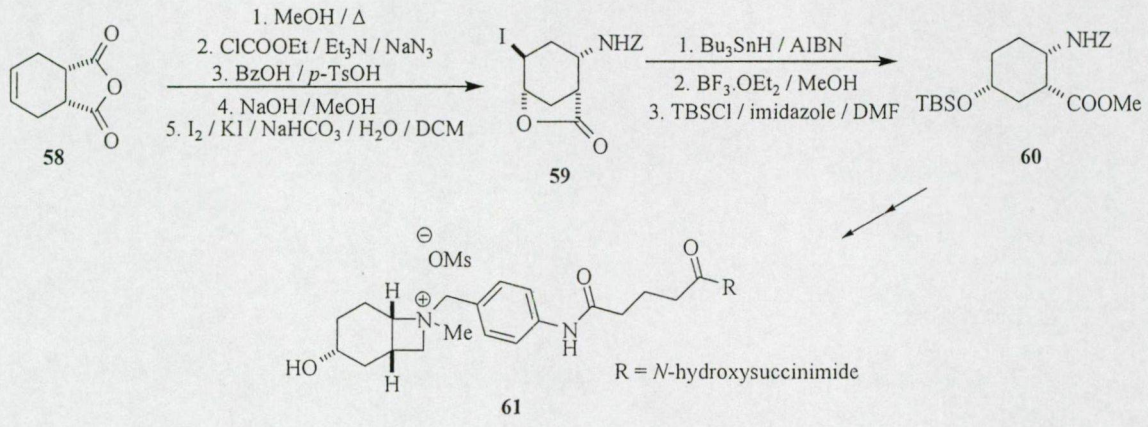
Scheme 12

Twenty years ago, Kobayashi *et al.* reported that the PLE-catalysed hydrolysis of the *meso* diester **49** quantitatively furnished the monoester **50** with an excellent enantiomer excess (*ee* > 96%).[50] The chiral monoester **50** was then converted to the *β*-amino ester **51,** which was hydrolysed with trifluoroacetic acid, and the resulting carboxylic group of **52** was subjected to iodolactonization in a two-phase system, yielding the iodolactone **53**. Dehalogenation of **53** with DBU afforded the bicyclic lactone **54**. *N*-Methylation of **54** to **55** was cleanly achieved through the use of methyl iodide and silver oxide. Methanolysis of the lactone **55** gave the allyl alcohol **56**. This compound was the key intermediate in the enantioselective synthesis of (-)-fortamine (**57**) (Scheme 13).[6,29]



Scheme 13

Masemune *et al.* prepared hydroxy amino acid derivative **60** starting from anhydride **58** according to Scheme 14.[51] The anhydride **58** was converted to the iodolactone **59** in five steps, similarly to the method of Kobayashi *et al.*[6] The iodolactone **59** was reduced with tributyltin hydride, followed by treatment with boron trifluoride etherate and tributylsilyl chloride to give hydroxyamino ester **60**. This compound was utilized in the diastereoselective synthesis of hapten **61** and its inhibitor.[51]

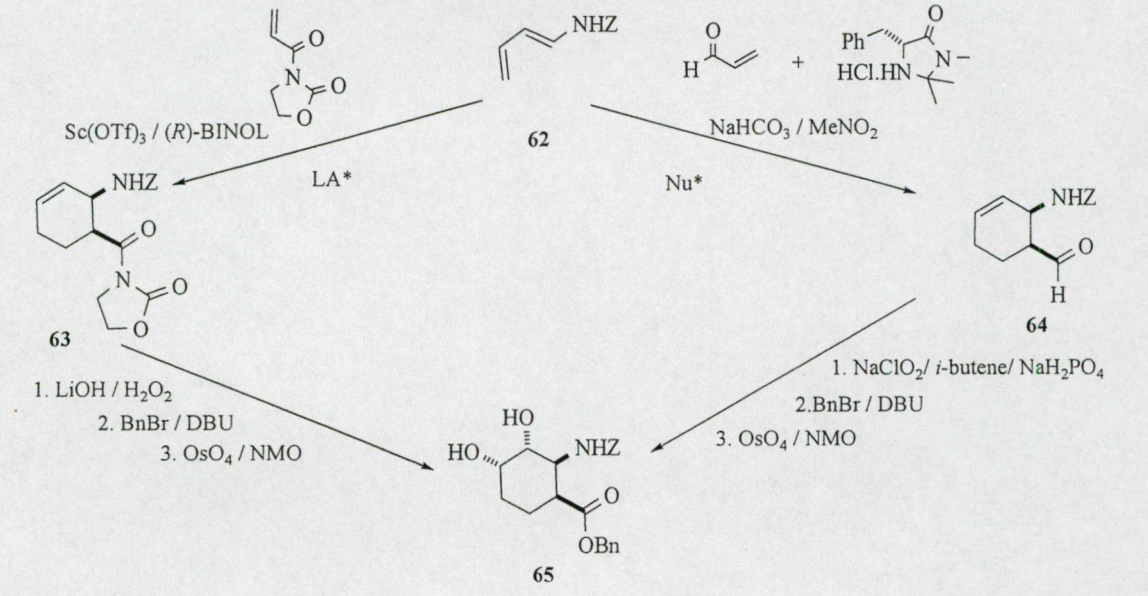


58 59 60 61

Scheme 14

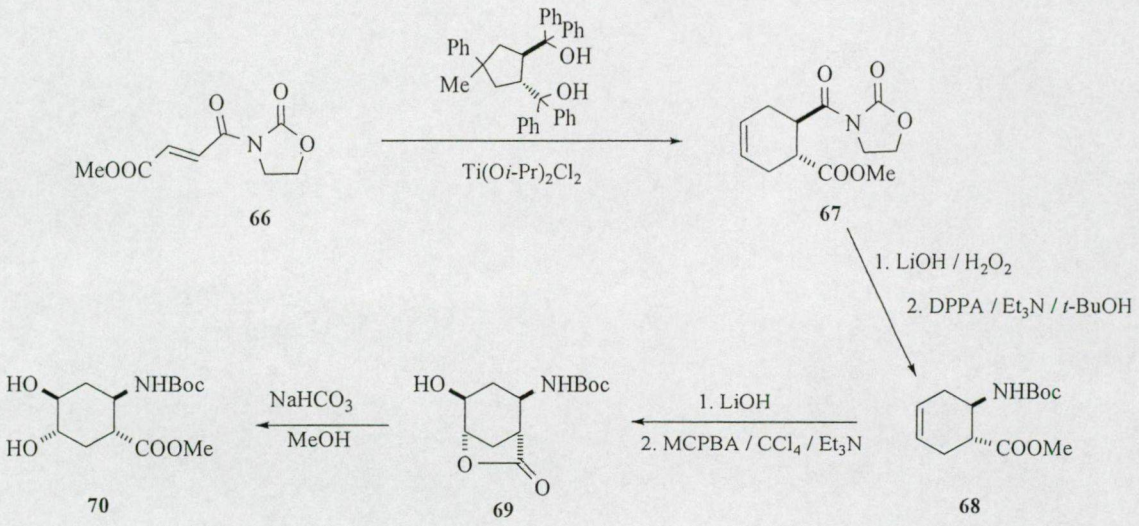
Wipf and Wang elaborated three efficient stereocontrolled Diels-Alder approaches towards dihydroxylated *cis*- and *trans*-aminocyclohexanecarboxylates.[52] Starting from *N*-benzyloxycarbonyl-protected aminodiene **62,** using Kobayashi's chiral scandium catalyst for the Lewis acid-mediated reaction with acyl-1,3-oxazolidin-2-one, they isolated the *cis* product in high yield (92%) and good *ee* (90%). After the saponification of **63** and benzyl ester formation, dihydroxylation proceeded to give the desired diol **65**.

An alternative route to the synthesis of **65** was the addition of phenylalanine-derived imidazolidinone, as a nucleophilic catalyst to a mixture of aminodiene **62** and acrolein. This method provided cyclohexene derivative **64** as a 14:1 mixture of the *cis* and *trans* diastereomers, respectively. Pure **64** was converted to **65** by oxidation, esterification and dihydroxylation. Both chiral Lewis acid- and nucleophile-catalysed asymmetric Diels-Alder routes provided **65** in high ee (> 98%) (Scheme 15).



Scheme 15

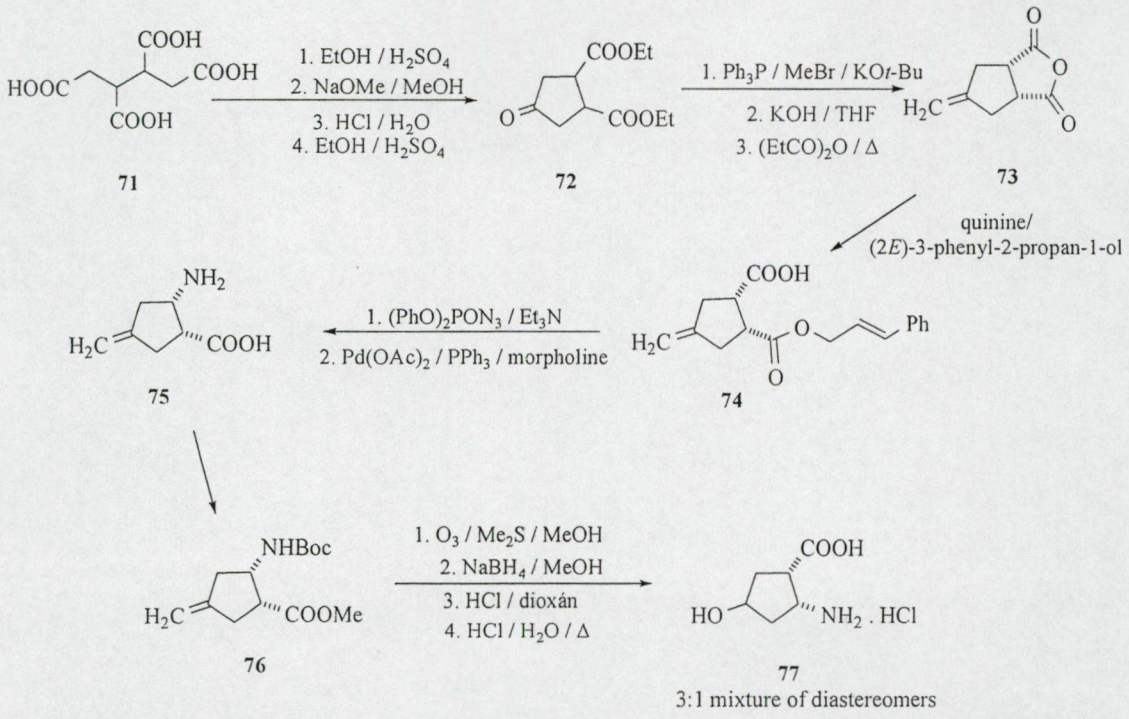
A combination of a titanium-catalysed asymmetric Diels-Alder reaction with fumarate hemi-ester **66,** followed by Curtius rearrangement and neighbouring group-assisted alkene functionalization, provided the hydroxy lactone **69** as a single diastereomer. Subsequent methanolysis gave the tetrasubstituted cyclohexane analogue **70** (Scheme 16).



Scheme 16

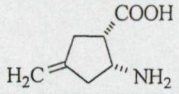
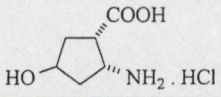
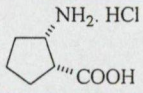
2.2.2.2. By transformation of other functional groups

A series of novel *β*-amino acids, including *cis*-2-amino-4-hydroxy-cyclopentanecarboxylic acid diastereomers **77**, have been synthetized and tested for their *in vitro* antifungal activity against *Candida albicans* by Mittendorf *et al.*[27,28] Compound **77** was prepared in a straightforward manner as depicted in Scheme 17. Commercially available butanetetracarboxylic acid (**71**) was converted in a four-step sequence to cyclopentanone diester **72** as a mixture of diastereomers (*trans/cis* = 5:1). The next step, a one-pot sequence of Wittig methylation and ester hydrolysis provided the dicarboxylic acid, mainly as the *trans* diastereomer (*trans/cis* = 50:1), which was completely isomerized to the *cis meso*-anhydride **73**. In the key step, a highly enantioselective quinine-mediated alcoholysis of the *meso*-anhydride **73** provided cinnamyl ester **74** with *ee* > 97%. Subsequent Curtius rearrangement and Pd-catalysed removal of the cinnamyl protecting group afforded **75** with *ee* > 99 %. 4-Hydroxy-amino acid diastereomers **77** were obtained from the protected *β*-amino acid **76** in four steps.



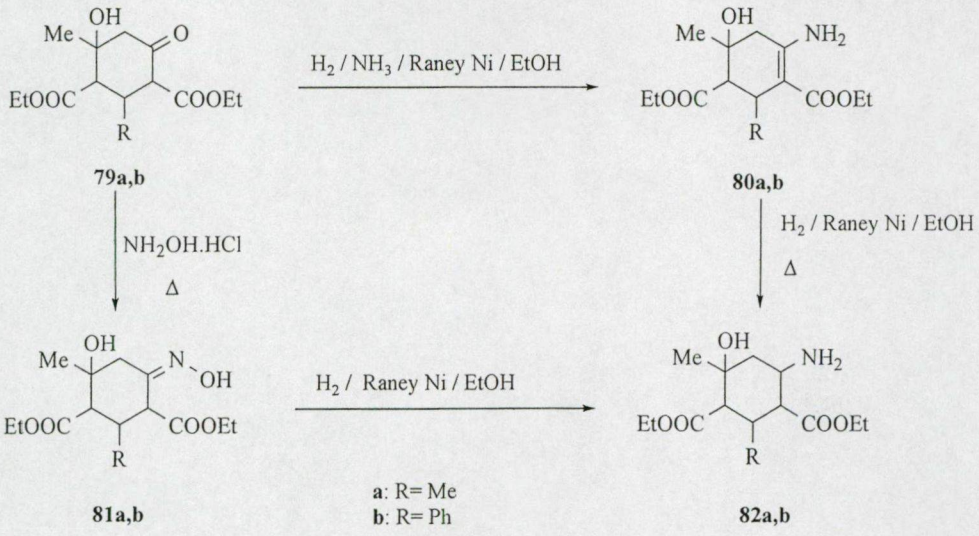
Scheme 17

Table 1 *In vitro* activity of *β*-amino acids against *Candida albicans*

Compound	Structure	IC_{50} (mg/L)
75		0.13
77[a, b]		128
78		0.13

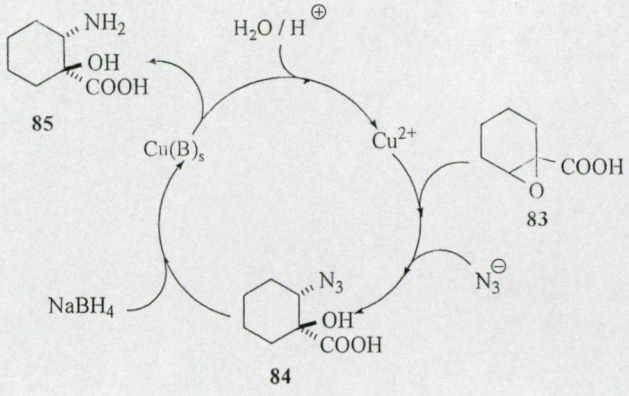
[a] Racemic; [b] mixture of diastereomers

Kachenko *et al.* prepared diethyl 6-amino-4-hydroxy-2,4-dialkyl-cyclohexane-1,3-dicarboxylic acid derivatives **82a,b** in good yields starting from oxoesters **79a,b**.[53] Oxoesters **79a,b** were reduced in the presence of ethanolic ammonia solution through enamino esters **80a,b,** or in the presence of hydroxylamine solution through oxime intermediates **81a,b** (Scheme 18). The relative configurations of the starting material, intermediates and final products were not fully characterized; the authors reported only elemental analysis and IR spectral data.



Scheme 18

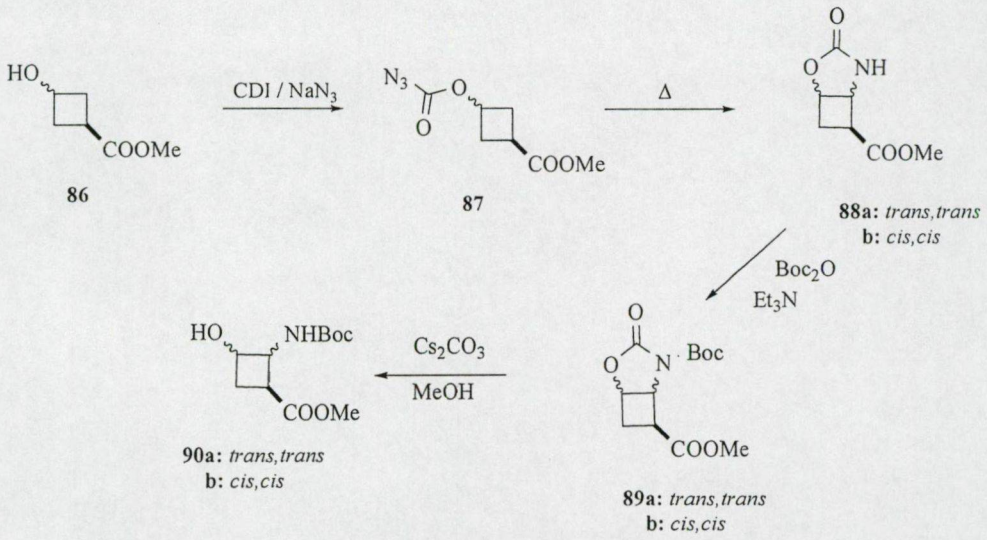
In 2003, Fringuelli *et al.* reported the first one-pot metal-catalysed synthesis of racemic and optically active α-hydroxy-β-amino acids by azidolysis of the corresponding α,β-epoxycarboxylic acids and the *in situ* reduction of the resulting β-azido-α-hydroxycarboxylic acid intermediates.[54] The same metal catalyst mediated both the oxirane ring opening by NaN_3 and the azido group reduction processes. The whole process was performed solely in water, without the use of any organic solvents. The amino acid derivatives were isolated in excellent yields. The authors prepared a number of open-chain and a single cyclic hydroxylated amino acid **85**. The azidolysis of cyclic epoxide **83** and the reduction of racemic azido compound **84** were fast (30 min each) and the copper nitrate catalyst was used in five cycles without loss of its efficiency (Scheme 19).



Scheme 19

2.2.2.3. Miscellaneous

An interesting method was developed by Hansen *et al.*, based on azidoformate ring closure to cyclobutane (Scheme 20).[55] A mixture of *cis*- and *trans*-hydroxy esters **86** was transformed to azidoformates **87,** which were thermally cyclized to oxazolidinones **88a** and **88b**. The *cis* and *trans* isomers were separated by chromatography. After Boc protection and careful cleavage of the carbamate functionality, 3-hydroxy-substituted *β*-aminocyclobutanecarboxylate isomers **90a** and **90b** were obtained. They were transformed to dipeptides and incorporated into a longer peptide sequence.



Scheme 20

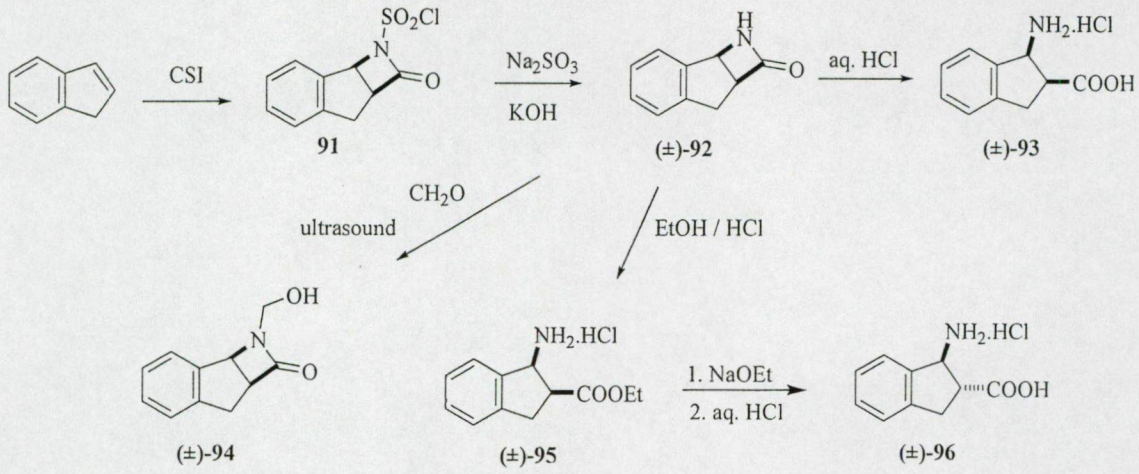
3. RESULTS AND DISCUSSION

3.1. Syntheses of new amino acids

3.1.1. Synthesis of 1-aminoindane-2-carboxylic acid, a new cispentacin benzologue

The reaction of CSI with different cycloalkenes is a well-known route for the synthesis of cycloalkane-fused β-lactams[56-58]. There are several examples in the literature for the regio- and stereospecificity of the cycloaddition, in accordance with the Markovnikov orientation of CSI addition.[59-61] For example, Murray and Cromwell[62] reported the synthesis of *cis*-*N*-chlorosulfonyl-3,4-benzo-6-azabiciclo[3.2.0]heptan-7-one (**91**). Hydrolysis of the sulfonyl chloride group with sodium bisulfite in the presence of sodium bicarbonate gave β-lactam **92** in relatively low yield (41%). This compound is a suitable precursor for the synthesis of 1-aminoindane-2-carboxylic acid. Our aim was the synthesis of all four enantiomers of 1-aminoindane-2-carboxylic acid, a new cispentacin benzologue.

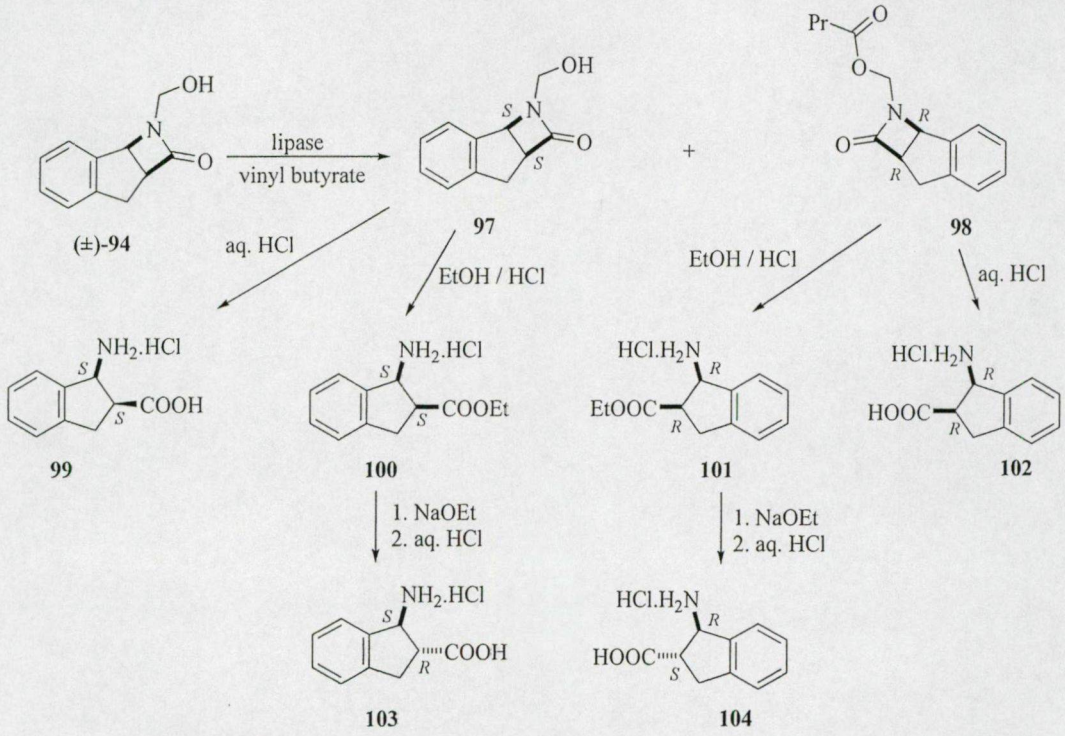
The pathways of the syntheses of the racemic amino acids **93** and **96** are shown in Scheme 21. Chlorosulfonyl isocyanate addition to indene takes places regio- and stereoselectively, resulting in *N*-chlorosulfonyl-β-lactam **91**. The general procedure of Murray and Cromwell was modified: The crystalline *N*-chlorosulfonyl-β-lactam **91** was dissolved in diethyl ether and added, with stirring, to a mixture of sodium sulfite in water and diethyl ether. During the addition, the aqueous phase was kept slightly alkaline by addition of potassium hydroxide. In this method, the yield (63%) was higher than described above. Treatment of **92** with hydrochloric acid resulted in amino acid hydrochloride **93**, while treatment with ethanolic hydrogen chloride led to ethyl ester **95**. Sodium ethoxide isomerization of **95**, followed by acidic hydrolysis, resulted in the *trans* amino acid hydrochloride **96**. The free amino acids of **93** and **96** were liberated by ion-exchange chromatography. The *N*-hydroxymethylated β-lactam **94**, the starting compound of the enzymatic reactions, was prepared from **93** with paraformaldehyde under sonication.



Scheme 21

The intermediate racemic hydroxymethylated *β*-lactam **94** was resolved through the lipase-catalysed asymmetric acylation of the primary hydroxy group at the (*R*) stereogenic centre. High enantioselectivities (E>200) were observed when the enzymatic reactions were performed with lipase AK or lipase PS as catalyst and vinyl acetate or vinyl butyrate as acyl donor. The hydrolysis and isomerization resulted in all four enantiomers (**99**, **102**, **103** and **104**) of 1-aminoindane-2-carboxylic acid, a new benzologue of cispentacin (Scheme 22).

X-ray investigation revealed the absolute configuration of **101**. Amino ester base **101** was transformed to the thiourea compound **105** by reacting it with (*1S,2S*)-1,3-diacetoxy-1-(4-nitrophenyl)-2-propyl isothiocyanate (DANI).[63,64] The X-ray structure (Fig. 1) clearly shows the (*R,R*) configuration of the starting **101**.



Scheme 22

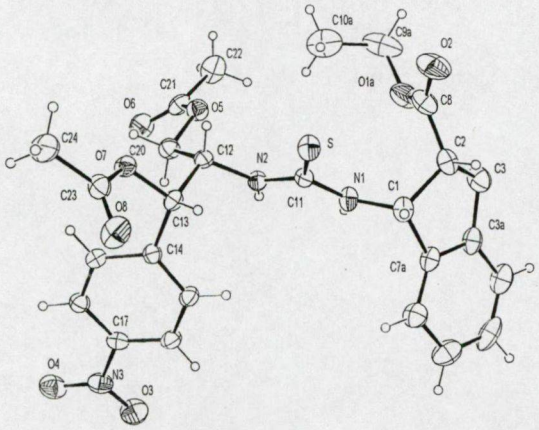


Figure 1 ORTEP plot of the X-ray structure of thiourea **105**

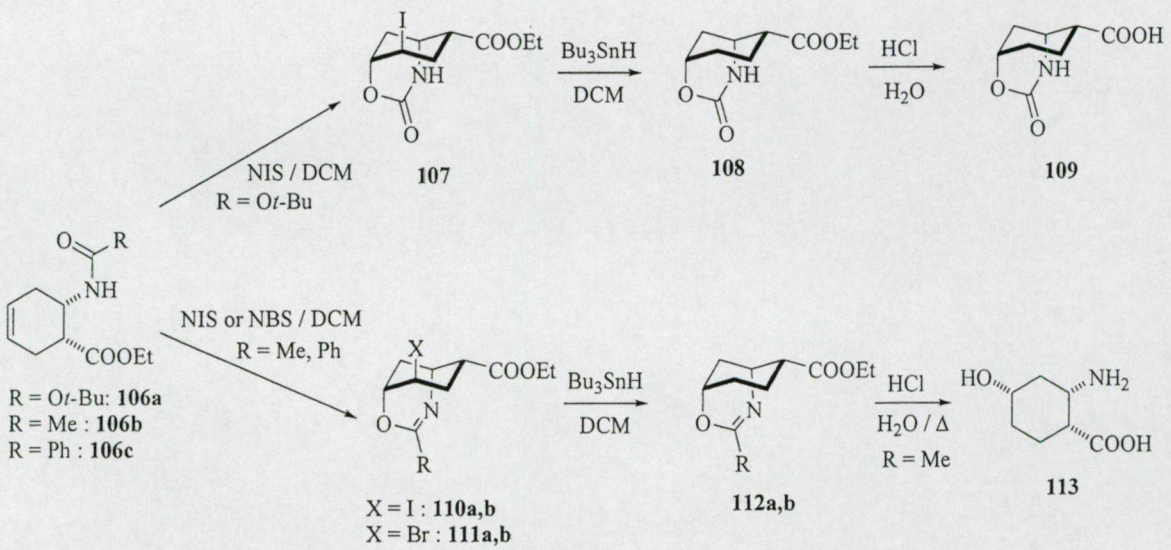
3.1.2. Syntheses of alicyclic hydroxy-β-amino acids

In recent years, a number of new syntheses of functionalized cyclic *β*-amino acid derivatives have been reported (see *e.g.* refs., 33, 46, 52, 54). Among them, hydroxy-substituted *β*-amino acids are of considerable importance because of their occurrence in many biologically active compounds (*e.g.* taxol and related molecules).[14-17] Our present aim was to introduce an extra hydroxy group at position 4 or 5 of the cyclohexane ring. For these syntheses, the readily available *cis*- and *trans*-2-amino-4-

cyclohexenecarboxylic acids were used. For the derivatization, we considered two strategies: cyclization on an acylamino derivative via 1,3-oxazine formation, or cyclization on a carboxylic acid function via lactone formation (iodolactonization protocol).

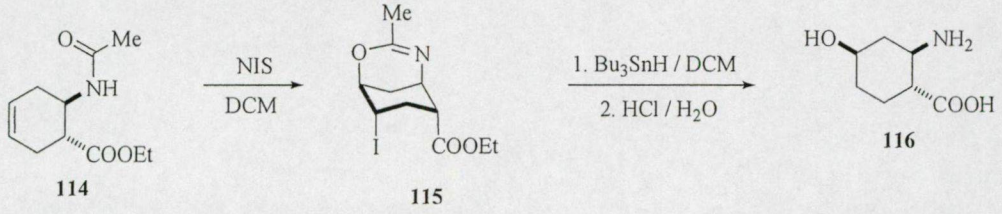
The starting *cis*-2-amino-4-cyclohexenecarboxylic acid was prepared by hypochlorite-mediated Hofmann degradation of the carboxamide obtained by ammonolysis of *cis*-1,2,3,6-tetrahydrophthalic anhydride.[65] The amino acid was esterified in the presence of ethanol and thionyl chloride, then acylated with *tert*-butoxy pyrocarbonate, acetic chloride or benzoyl chloride, resulting in *N*-acylated amino esters **106a-c**, respectively.

With *N*-iodo- (NIS) or *N*-bromosuccinimide (NBS) (for a related transformation, see *e.g.* ref. 66), the *N*-Boc derivative **106a** gave oxazinone **107**, while the *N*-acetyl and *N*-benzoyl derivatives **106b** and **106c** furnished the corresponding methyl- or phenyl-substituted oxazines **110a,b** and **111a,b** regio- and diastereoselectively (Scheme 23). Not even traces of other regio- or diastereomers were observed in the crude product. Iodooxazinone **107** and bromo- or iodooxazine derivatives **110a,b** and **111a,b** were dehalogenated with tributyltin hydride under an argon atmosphere, resulting in compounds **108** and **112a,b**, respectively. Acidic hydrolysis of **108** gave the stable oxazinonecarboxylic acid derivative **109**, which slowly decomposed on further heating. Hydrolysis of oxazine **112b** with 20% aqeous HCl, and removal of the HCl by ion-exchange chromatography led to the *all-cis* isomer of 2-amino-4-hydroxy-cyclohexanecarboxylic acid **113**.



Scheme 23

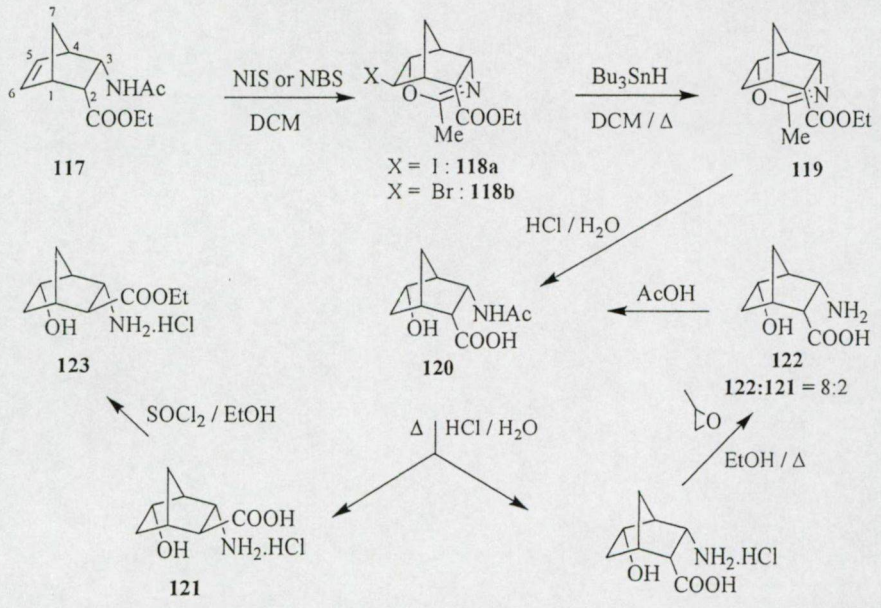
The corresponding *trans*-2-amino-4-cyclohexenecarboxylic acid was prepared by Hofmann degradation of the carboxamide obtained by ammonolysis of *trans*-1,2,3,6-tetrahydrophthalic anhydride. The amino acid was esterified, and subsequent treatment with acetic chloride resulted in *N*-acetylamino ester **114**. By a similar transformation as for the *cis* isomer **106b**, the *trans*-2-acetylamino-4-cyclohexenecarboxylic acid **114** reacted via the iodooxazine intermediate **115** to furnish the corresponding (*r*-1,*t*-2,*t*-4)-2-amino-4-hydroxycyclohexanecarboxylic acid **116** (Scheme 24).



114 **115** **116**

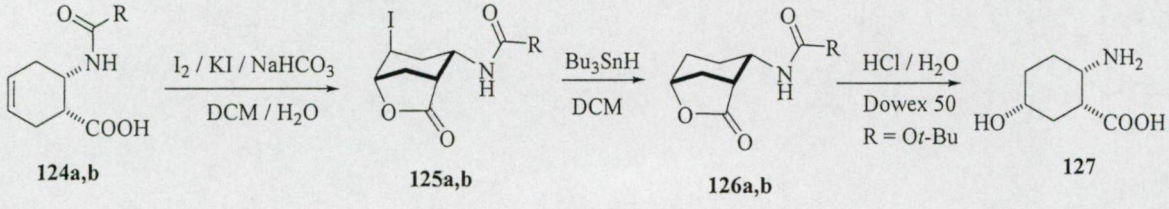
Scheme 24

For the synthesis of the corresponding norbornane derivatives, *endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid[67] derivative **117** was chosen. When *N*-acetylamino ester **117** was reacted with NIS or NBS, tricyclic 1,3-iodo- or bromooxazine derivative **118a,b** was obtained, stereoselectively. Iodo- or bromooxazine derivative **118a,b** underwent dehalogenation with tributyltin hydride under an argon atmosphere, resulting in compound **119**. Hydrolysis of oxazine **119** with dilute HCl at room temperature gave the *N*-acetyl-hydroxy amino acid **120**. When *N*-acetyl-hydroxy amino acid **120** was boiled in acidic solution, *endo* → *exo* isomerization took place and the forced conditions resulted in 3,5-*diendo*-2-*exo*-3-amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride (**121**) as the main product. The mother liquor was treated with a large excess of propylene oxide, and after fractional crystallization compound **122** was also isolated as a diastereomerically enriched (8:2) mixture (Scheme 25). The correct configuration of the hydroxylated amino acids **121** and **122** was proved indirectly, the stereostructures of **120** and **123** being established via a DIFFNOE technique and also by chemical transformation: esterification of **121** led to hydroxylated amino ester **123**, while **122** after acetic acid treatment gave an *N*-acetyl derivative. The NMR spectra of the resulting compound was identical with those of *all-endo*-3-acetylamino-5-hydroxybicyclo-[2.2.1]heptane-2-carboxylic acid (**120**).



Scheme 25

Stereoselective iodolactonization[6] was the key step in the synthesis of 2-amino-5-hydroxycyclohexanecarboxylic acid. The reactions of *N*-benzoyl- and N-Boc-protected *cis*-2-amino-4-cyclohexenecarboxylic acid **124a,b** with I_2/KI in slightly alkaline medium yielded iodolactones **125a,b** in fairly good yields, with excellent regio- and diastereoselectivity; the products were reduced with tributyltin hydride to give lactones **126a,b**. The acidic hydrolysis of benzoyl derivative **126a** did not give the desired amino acid; instead, decomposition took place. When the *N*-Boc lactone **126b** was hydrolysed after ion-exchange chromatography, the *all-cis* isomer of 2-amino-5-hydroxycyclohexanecarboxylic acid **127** was obtained in 66% yield (Scheme 26).



R = Ph :**a**; R = O*t*-Bu : **b**

Scheme 26

X-ray diffraction studies confirmed the structure of **127**. All the bonding parameters were in the usual ranges. The molecular structure and extensive hydrogen bonding system of **127** are presented in Fig. 2.

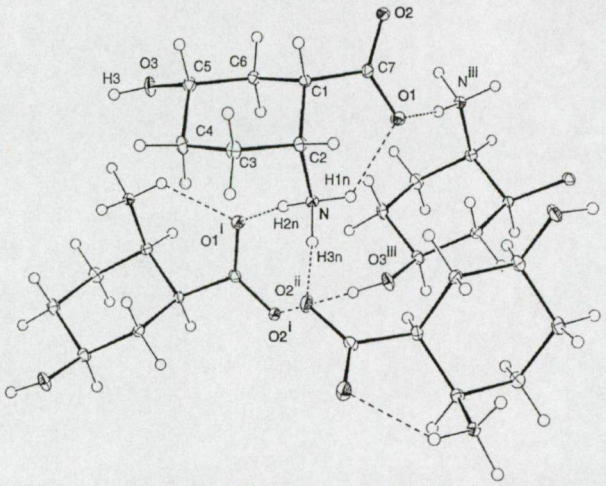
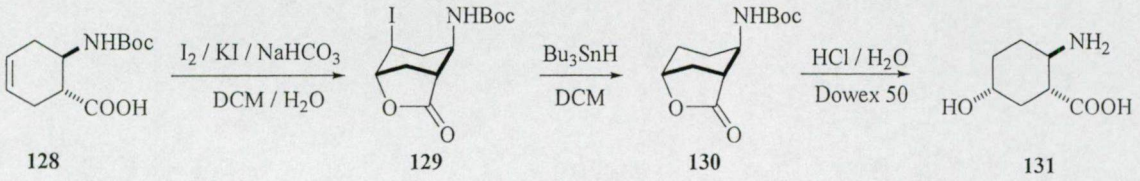


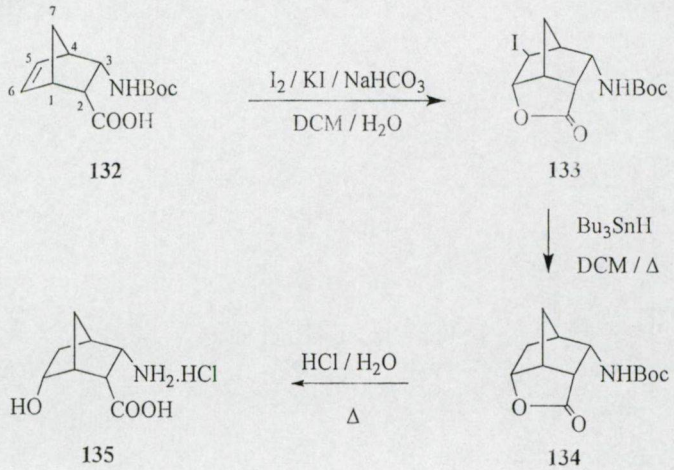
Figure 2 Crystal structure of **127,** showing the hydrogen bonding scheme

By a similar transformation, from *trans*-2-*tert*-butoxycarbonylamino-4-cyclohexenecarboxylic acid (**128**) via iodolactone **129**, the corresponding (*r*-1,*t*-2,*c*-5)-2-amino-5-hydroxycyclohexanecarboxylic acid (**131**) was prepared (Scheme 27).



Scheme 27

By the same method the corresponding *all-endo*-3-amino-6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid (**135**) was obtained from *N*-Boc-*endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**132**) (Scheme 28). The given stereochemistry and the relative configurations of the synthetized compounds (**106-135**) were proved by using certain key vicinal couplings and characteristic NOEs.



Scheme 28

The syntheses of enantiomeric *cis* compounds (+)-**113** and (-)-**127** were performed from *rac*-7-azabicyclo[4.2.0]oct-3-en-8-one by CAL-B treatment with one equivalent of H_2O in isopropyl ether as described earlier.[68] The enantiopure β-lactam obtained was transformed with 18% HCl into the (1*S*,2*R*)-2-amino-4-cyclohexenecarboxylic acid hydrochloride.[68] The syntheses of 4-hydroxy- and 5-hydroxyamino acid enantiomers (+)-**113** and (-)-**127** were carried out similarly as for the racemic compounds given in Schemes 23 and 26, resulting in the products with *ee* ≥98%.

3.2. Ring-closure reactions of alicyclic β-amino acid derivatives

3.2.1. Synthesis and mild retro Diels-Alder decomposition of 1,4-methanopyrrolo-, 1,4-methanopyrido- and 1,4-methanoazepino[2,1-b]-quinazolinones

Fused pyrimidinones are widely-used sources for the synthesis of new potential therapeutic agents.[69-73] The pyrrolo- and pyrido[2,1-*b*]quinazolinones include well-known alkaloids isolated from a number of families of plants. *Adhatoda vasica* containing vasicine (peganine) has been used in Indian indigenous medicine for centuries. Because of their therapeutic interest, the syntheses of pyrido[2,1-*b*]quinazolin-11-one derivatives and their ring **A** and **C** homologues have been studied very thoroughly.[71-73] Although numerous papers deal with the synthesis of pyrido[2,1-*b*]quinazolin-11-ones and their differently saturated analogues and homologues, the corresponding norbornane- and norbornene-fused derivatives **141-144** are not known.

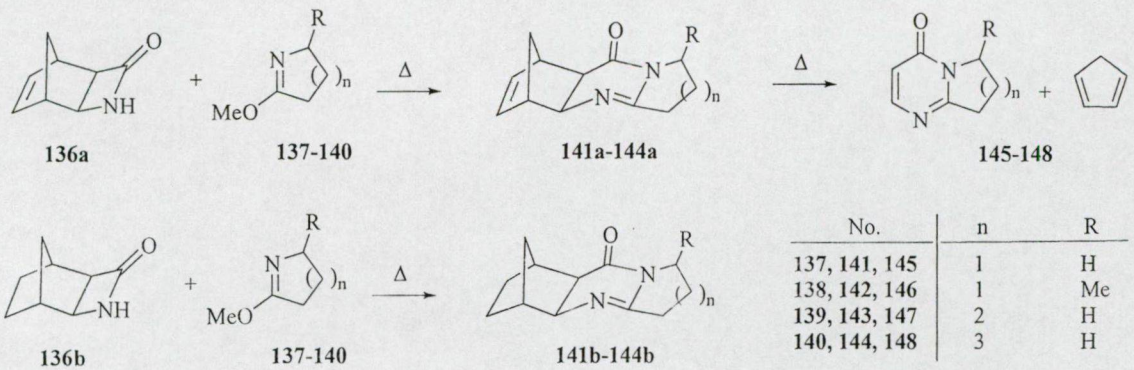
In the first experiments for the synthesis of tetracycles **141-144**, 3-*exo*-aminobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid[74] or the corresponding saturated derivative or either of the ethyl esters was refluxed in chlorobenzene with 2 equivalents of lactim ethers **137-140**, as described for the synthesis of *cis*- and *trans*-decahydropyrido[2,1-*b*]quinazolin-11-one.[75] After refluxing for 24 h, the starting materials were recovered unchanged. When azetidinones[74,76] **136a** and **136b** were reacted in chlorobenzene with lactim ethers, a very slow transformation was observed, and the reaction mixture turned deep-brown.

On melting of the azetidinones **136a** and **136b** with 2 equivalent of lactim ethers **137-140** at 80 °C for 8-10 h, the desired tetracycles **141a,b-144a,b** were obtained. The first step of the reaction is the formation of an amidine intermediate which, after transamidation,[77] results in the ring-enlargement products **141a,b-144a,b.** On increase

of the temperature, the colour of the reaction mixture becomes deeper, and in the series **136a** the smell of cyclopentadiene is observed. Following the melting of **136a** with **138** at 100 °C, 6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-one (**146**) was isolated in low yield through the splitting-off of cyclopentadiene. Retrodiene decomposition under similarly mild conditions was described only recently for the synthesis of monocyclic 1,3 derivatives.[78] The bicyclic hetero compounds pyrimido[2,1-*b*]thiazin-6-one and thiazolo[3,2-*a*]pyrimidin-5-one have also been prepared by this method.[79]

In order to establish the scope and limitations of this retrodiene decomposition resulting in heterobicycles, tetracycles **141-144** were melted at 100 °C. When **141a-144a** were melted for 30 min, pyrrolo-, pyrido- and azepino[1,2-*a*]pyrimidinones **145-148** were formed in good yield, by the splitting-off of cyclopentadiene. Starting from the series **141b-144b**, the formation of **145-148** could not be observed under similar conditions (Scheme 29).

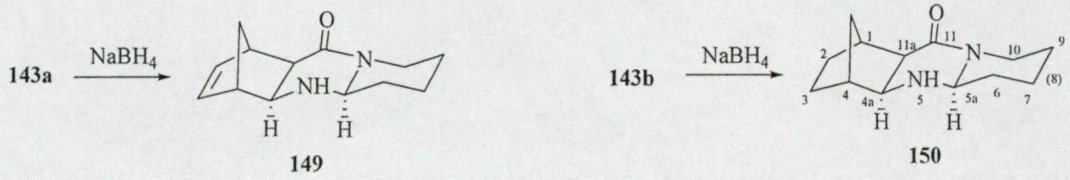
Because of their pharmacological interest,[80] a number of different routes have been devised for the synthesis of substituted analogues of **145-148**. Our method is a new, effective procedure for the preparation of the above derivatives.



No.	n	R
137, 141, 145	1	H
138, 142, 146	1	Me
139, 143, 147	2	H
140, 144, 148	3	H

Scheme 29

Sodium borohydride reduction of **143a** resulted stereospecifically in the decahydro derivative **149** with relative configuration *r*-1,*c*-4,*c*-4a,*c*-5a,*c*-11a. When **143b** was reduced with sodium borohydride, the perhydro derivative **150** was formed (Scheme 30). Their similar relative configurations were proved both spectroscopically and chemically: catalytic reduction of **149** gave a compound identical with the product of **150**. Attempted retrodiene decomposition from both **149** and **150** was unsuccessful. The successful and failed retro Diels-Alder reactions show that a retrodiene decomposition takes place under mild conditions only when the decomposition results in a heterocycle with a quasi-aromatic character through the splitting-off of cyclopentadiene.



Scheme 30

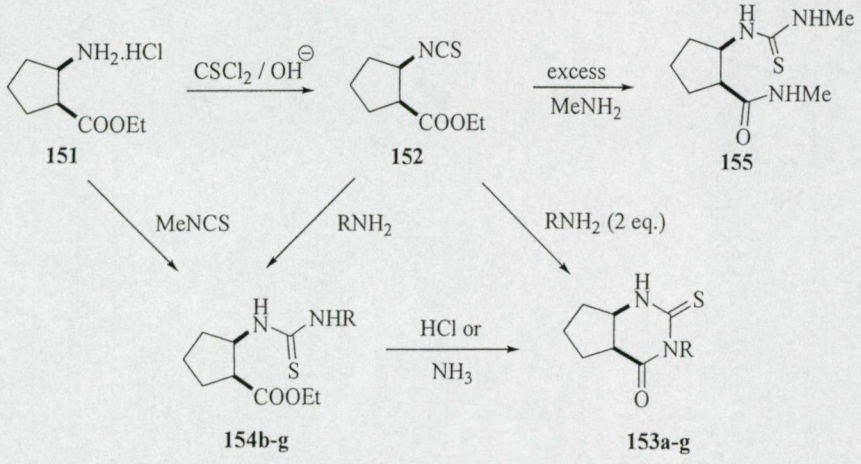
3.2.2. Synthesis and transformations of stereoisomeric ethyl 2-isothiocyanato-1-cyclopentanecarboxylates

Isocyanato and isothiocyanato compounds are widely used for the preparation of ureas, thioureas and heterocyclic derivatives,[81] which have a wide range of biological activities.

cis-2-Aminocyclopentanecarboxylic acid was prepared from cyclopentene by addition of CSI and subsequent ring opening of the resulting azetidinone with hydrochloric acid.[82] The *trans* isomer was obtained by the addition of ammonia to 1-cyclopentene-1-carboxylic acid.[83] The amino acids were transformed to the amino ester hydrochlorides **151**[84] and **156**[85] with thionyl chloride and ethanol. Ethyl *cis*- and *trans*-2-isothiocyanato-1-cyclopentanecarboxylates **152** and **157** can be prepared through reaction of the ester hydrochlorides **151** and **156** with thiophosgene in the presence of sodium hydrogencarbonate at 40 °C and subsequent column chromatography of the crude oily products (Schemes 31 and 32).

Isocyanates **152** or **157** were reacted with different amines and, depending on the reagents, the ratio of the reactants and the configuration of the isothiocyanate, three different products were formed. The *cis* **152** with two equivalents of ammonia or methylamine gave the corresponding 2-thioxo-1,2,3,4a,5,6,7,7a-octahydro-cyclopenta[*d*]pyrimidin-4-ones **153a** and **153b**, respectively. When an excess of ammonia was used, the product was again **153a**, but with an excess of methylamine the *cis* **152** gave the thiourea **155**: the ester was amidated rather than ring closure occurring.

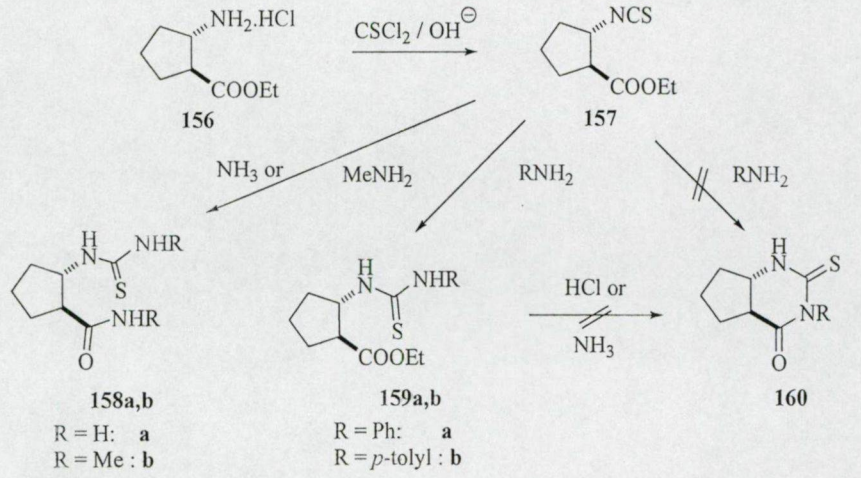
Reactions of substituted amines such as isopropylamine, benzylamine, phenylethylamine, aniline and *p*-toluidine with **152** resulted in the corresponding thioureas **154c-g**. Thiourea **154b** was prepared from **151** with methyl isothiocyanate as described earlier.[86] Thioureas **154** can readily be cyclized using either acidic (HCl) or basic (*e. g.* NH_3) catalysts.



R = H: **a**; Me: **b**; *i*-Pr: **c**; Ph: **d**; CH_2Ph: **e**; CH_2CH_2Ph: **f**; *p*-tolyl: **g**

Scheme 31

When the *trans* **157** ester isothiocyanate (Scheme 37) was reacted with amines, formation of the pyrimidinone **160** was not observed, even under forcing conditions. However the reaction with ammonia or methylamine led to the thiourea-amide derivatives **158a,b**. With aniline or *p*-toluidine, the *trans* thioureas **159a** and **159b** were formed in good yields. The cyclization of *trans* thioureas **159a** and **159b** failed under both acidic and basic conditions.



Scheme 32

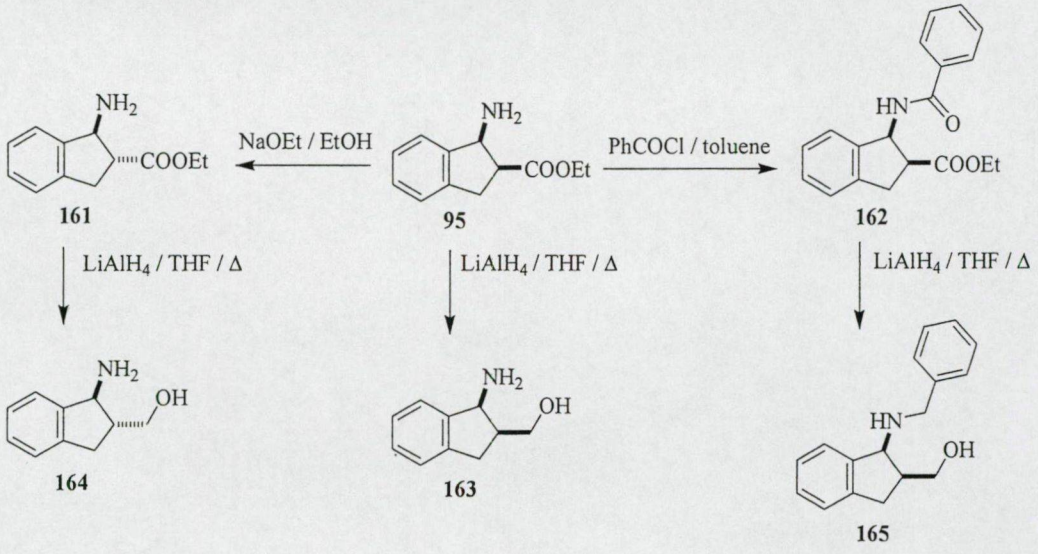
It is noteworthy that in the ring closures of the 1,2-disubstituted-1,3-difunctional cyclohexane, cycloheptane and cyclooctane derivatives, no appreciable differences were found in the reactivities of the *cis* and *trans* isomers in the formation of six-membered 1,3-heterocycles fused with carbocycles.[8,87] In contrast, very striking differences were observed in the cyclization reactivities of the *cis*- and *trans*-1,2-disubstituted 1,3-difunctional cyclopentane derivatives, such as 2-hydroxymethyl-1-cyclanols and alicyclic 2-aminomethyl-1-amines, or in the cases of *cis*- and *trans*-2-hydroxy-1-cyclopentanecarboxamides or *cis*- and *trans*-2-aminocyclopentanecarboxylic acids. The

cis isomers react readily, while their *trans* counterparts do not undergo ring closure in most cases.

The differences observed in the present study may serve as supporting evidence for the differences in the ring-closure reactivities of *cis*- and *trans*-1,2-disubstituted 1,3-difunctional cyclopentane derivatives.[8]

3.2.3. Synthesis of indano[1,2-d][1,3]oxazines and thiazines, new ring systems

With racemic ethyl *cis*- and *trans*-1-aminoindane-2-carboxylate (**95** and **161**) available, our present aim was to prepare *cis*- and *trans*-1-amino-2-hydroxymethylindane and to examine the chemistry and stereochemistry of indane-fused 1,3-oxazines and thiazines. The *cis*- and *trans*-unsubstituted and *cis*-*N*-benzyl-substituted 1,3-amino alcohols **163-165** were prepared by $LiAlH_4$ reduction or by benzoylation followed by reduction, respectively (Scheme 33).



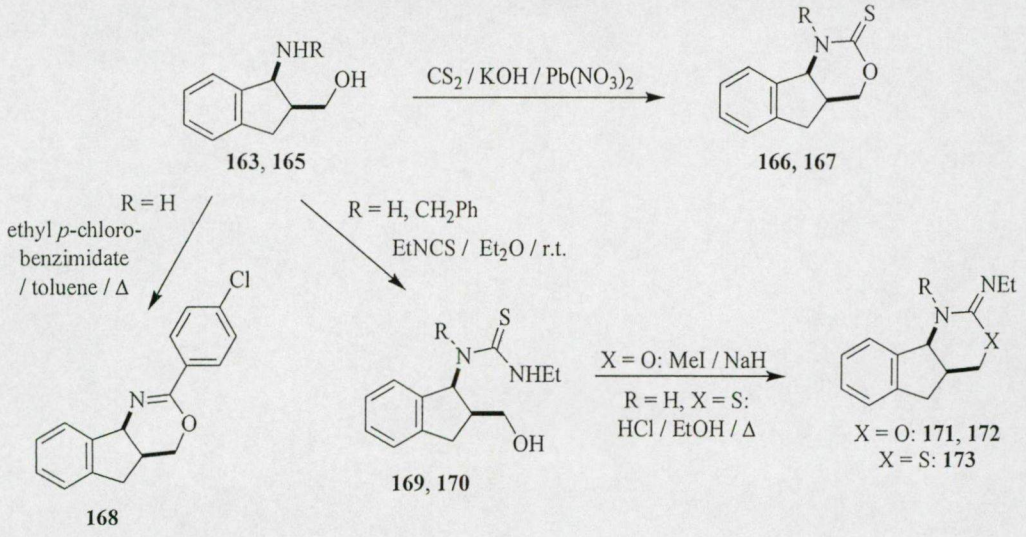
161 **95** **162**

164 **163** **165**

Scheme 33

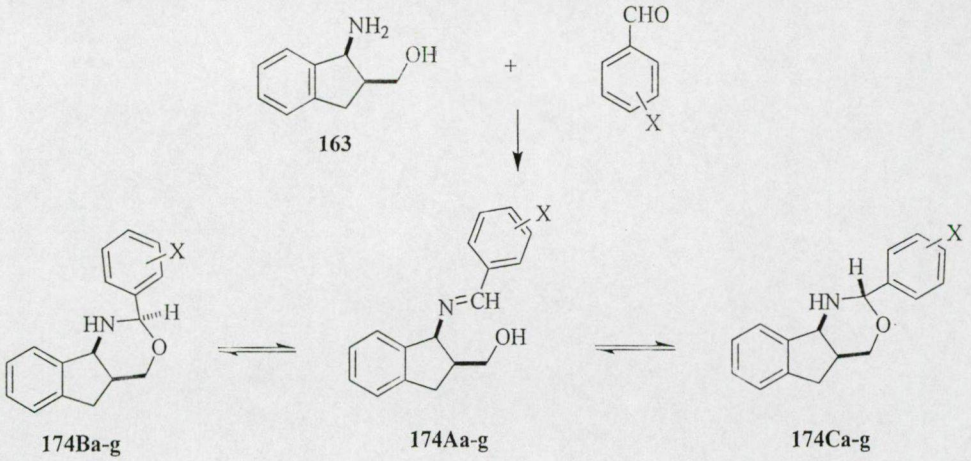
For the preparation of 2-thioxo-1,3-oxazines **166** and **167** the most common method is the reaction of the appropriate 1,3-amino alcohols **163** and **165** with carbon disulfide, followed by cyclization of the resulting thiourea with lead(II) nitrate. Cyclization of the corresponding 1,3-amino alcohol **163** with ethyl *p*-chlorobenzimidate resulted in the dihydro-1,3-oxazine **168**. The synthesis of heterocycles **171-173** started from the adducts of the corresponding amino alcohols **163** and **165** with ethyl isothiocyanate. Treatment of thioureas **169** and **170** with methyl iodide followed by alkali treatment led to the elimination of methyl mercaptan, resulting in the oxazines

171 and **172** in good yields. Treatment of thiourea **169** with ethanolic hydrogen chloride under reflux, followed by treatment with alkali, provided thiazine **173** (Scheme 34).



Scheme 34

The *cis* amino alcohol **163** was condensed in methanolic solution with seven substituted aromatic aldehydes with different electronic characters. The reactions reached completion within a few hours, even at room temperature. After evaporation and purification, well-defined products **174a-g** were obtained, which existed as three-component tautomeric mixtures in $CDCl_3$. For the tautomeric equilibria to be reached, the substances were allowed to stand for 24 h in $CDCl_3$ (Scheme 35). The relative configurations of the various structures **174A,B,C** were determined via the NOESY spectra, on the basis of the observation of NOEs between the NH-C*H*Ar-O and the NH-C*H*-CH hydrogen atoms.



X = *p*-NO_2: **a**; *m*-Br: **b**; *p*-Cl: **c**; H: **d**; *p*-Me:**e**; *p*-OMe: **f**; *p*-NMe_2: g

Scheme 35

Comparative studies were carried out earlier on the ring-chain tautomerism of a wide range of 2-aryl-substituted tetrahydro-1,3-oxazines.[58,88-92] For all these series, the following equation is valid:

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad (1)$$

where K_X = [ring]/[chain] and ρ is a constant characteristic of the ring system. In $CDCl_3$ at ambient temperature, ρ is 0.76 for tetrahydro-1,3-oxazines. When eq. (1) was applied to the log K_X values, good linear correlations were obtained *vs* the Hammett-Brown parameter (σ^+) of the substituent X on the 2-phenyl group for compounds **174a-g** (Tables 2 and 3, Fig. 3). The tautomeric ratios are based on the integration of the **174B** and **174C** ring form NH-C*H*Ar-O and the **174A** chain form N=CH proton singlets.

The linear regression analysis data in Table 3 show that, as customary among 2-aryl-substituted tetrahydro-1,3-oxazines, the value of ρ is positive in each case, *i.e.* an electron-withdrawing substituent on the 2-aryl ring favours the ring-closed tautomer. The proportion of the ring form for the *trans*-2-aryl-1,3-*O,N* heterocycles **174C** varies within a somewhat wider range (10.7-54%) than that for the corresponding *cis*-2-aryl-1,3-*O,N* heterocycles **174B** (9.2-41.7%). The relative configuration of the ring-closed products does not seem to influence the value of ρ: *cis*- and *trans*-2-aryl-1,3-*O,N* heterocycles have very similar values of ρ (0.78 and 0.81).

Table 2 Proportions (%) of ring forms (**B** and **C**) in tautomeric equilibria for compounds **174a-g** in $CDCl_3$ at 300 K

Compound	X	σ^+	**B** (%)	**C** (%)
174a	*p*-NO_2	0.79	41.7	54.0
174b	*m*-Br	0.05	39.3	49.8
174c	*p*-Cl	0.114	35.8	50.5
174d	H	0	35.1	41.5
174e	*p*-Me	-0.31	29.6	35.9
174f	*p*-OMe	-0.77	22.9	28.2
174g	*p*-NMe_2	-1.7	9.2	10.7

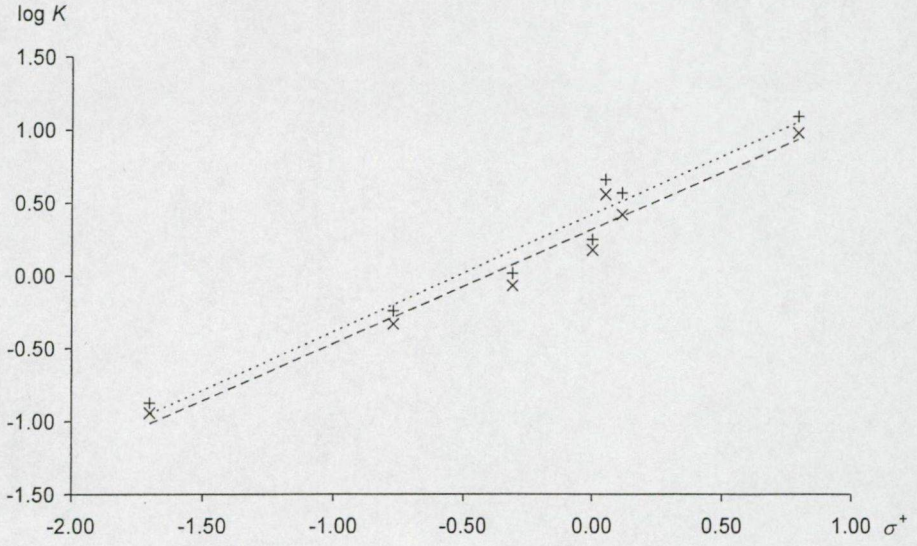


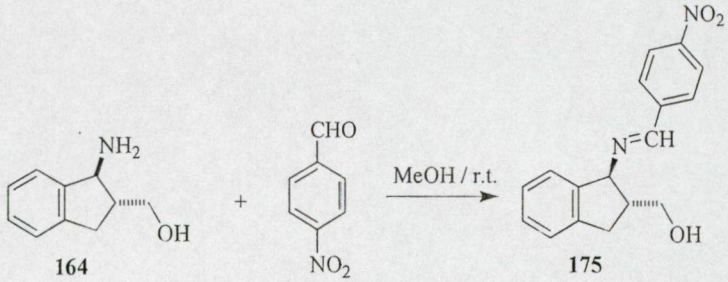
Figure 3 Plots of log K_X *vs* σ^+ for compounds **174a-g**: **B** (X), **C** (+) in $CDCl_3$

Table 3 Linear regression data for compounds **174a-g**

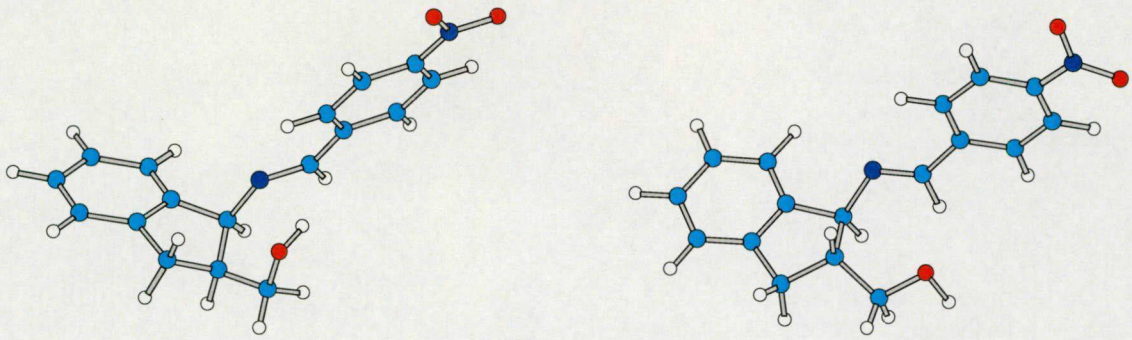
	B	**C**	[89]
Intercept	0.32	0.42	0.22
Slope	0.78	0.81	0.72
Corr. coeff.	0.981	0.979	0.991
No. of points	7	7	6

[89] The data for the corresponding cyclopentane-fused tetrahydro-1,3-oxazines

When the *trans*-amino alcohol **164** was condensed in methanol with *p*-nitrobenzaldehyde, a well-defined product was obtained, which exists solely as the open, Schiff base form **175** (Scheme 36). In this case, the OH group is too far from the N=CH bond (4.5 Å), and intramolecular proton transfer is not possible without energy transfer (Fig. 4)



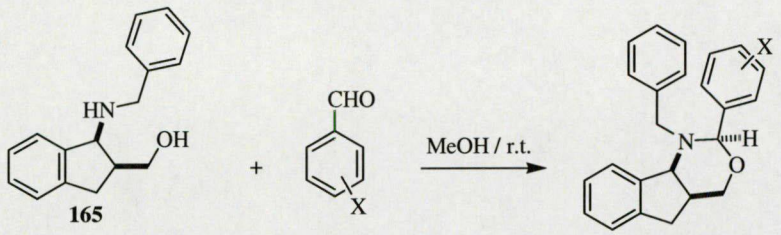
Scheme 36



174Ad **175**

Figure 4 Stereoview of typical minimum energy molecular structures for **174Ad** and **175**

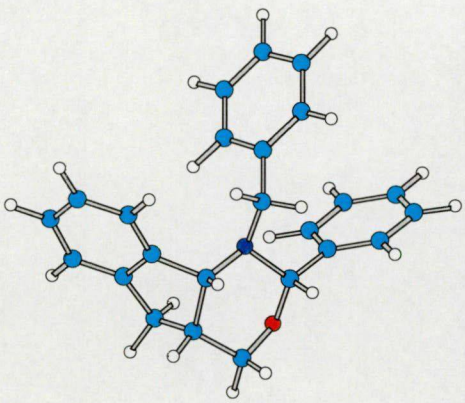
When the *N*-benzylamino alcohol **165** was condensed with aldehydes in methanolic solution at room temperature, only one diastereomer **176a-c** was observed in the $CDCl_3$ solution of the product at 300 K (Scheme 37). The product formed is stabilized by aromatic-aromatic interactions (Figure 4).



165 **176a-c**

X = *p*-NO_2: **a**; H: **b**; *p*-NMe_2: **c**

Scheme 37



176b

Figure 5 Stereoview of typical minimum energy molecular structure for **176b**

3.2.4. Synthesis of imidazo[1',5':1,2]pyrido[3,4-b]indole derivatives

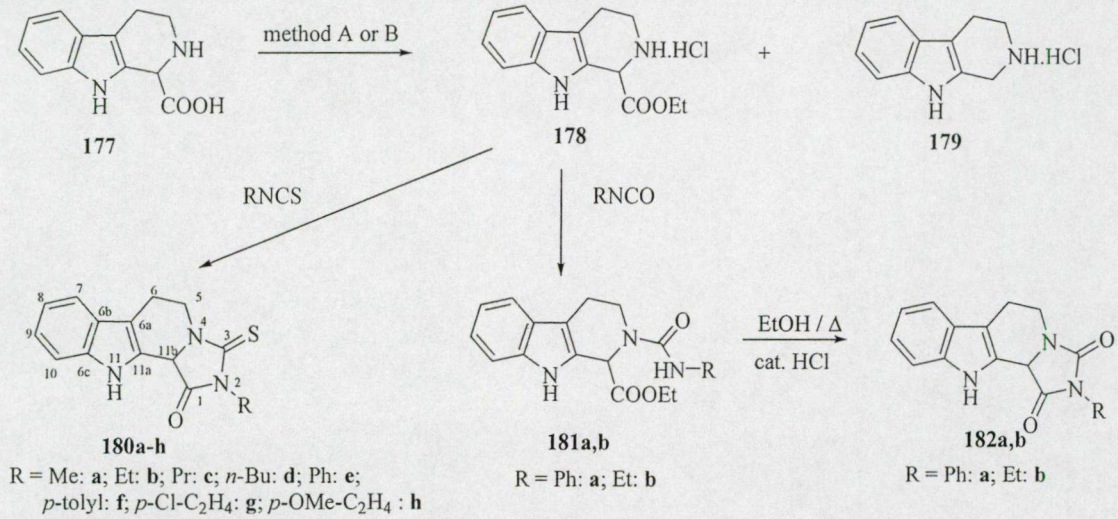
The β-carboline structure is present in important natural compounds, and its derivatives exert various pharmacological effects on the benzodiazepine receptors in the mammalian central nervous system. In 1994, in a programme with the goal of developing new drugs affecting the central nervous system, Lopez-Rodrigez *et al.* studied the possibilities of ring-closure of the 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (**177**) with alkyl and aryl isothiocyanates under vigorous conditions (refluxing for 40 h in acetone or DMSO). In their case, the corresponding hydantoin analogues were formed.[93] Some further derivatives of the 4-ring hydantoins exert pharmacological effects on α_1-adrenoreceptors.[94] However, the synthesis of thiohydantoin derivatives remained unsolved under the circumstances applied: in the reactions of **177** and isothiocyanates, decarboxylation took place, and open-chain thiourea derivatives were isolated instead of the desired thiohydantoins.

Our present aim was to attempt the synthesis of thiohydantoin-fused imidazo[1',5':1,2]pyrido[3,4-*b*]indole derivatives under mild conditions, based on the results of similar ring closures,[8] starting from ethyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**178**).

1,2,3,4-Tetrahydro-β-carboline-1-carboxylic acid (**177**) was obtained from tryptamine hydrochloride and glyoxylic acid.[95] Racemic **177** was esterified by two methods (Scheme 38): refluxing in ethanol with thionyl chloride (method A) or reaction with dry hydrogen chloride gas in ethanol (method B). Besides **178,** both methods resulted in a by-product, the hydrochloride of 1,2,3,4-tetrahydronorharmane (**179**) as a consequence of decarboxylation. This side-product could be filtered off from the hot ethanolic solutions. Method A gave a somewhat higher yield (A: 76%, B: 57%).

When the ester base **178** was combined with alkyl and aryl isothiocyanates at room temperature in methanol, the corresponding target thiohydantoins **180** could be filtered off from the reaction mixtures after stirring overnight. No decarboxylation was observed during the reactions, and no intermediates or by-products could be isolated from the residues. From the reactions of **177** and isothiocyanates under the same conditions, but with sodium methylate as the catalyst, the thiohydantoins **180** were obtained in rather low yields. The structures of the thiohydantoin compounds **180a-h,** involving two conformers and the presence of keto-enol tautomerism, were determined by NMR spectroscopy. In the reactions of **178** and ethyl and phenyl isocyanates under similarly mild conditions, the corresponding urea derivatives **181a,b** were formed as

crystalline products. These were cyclized by refluxing in ethanol for 1 day under hydrochloric acid catalysis. Hydantoin compounds **182a** and **182b** were formed in medium yield, and no other products could be isolated.



Scheme 38

3.3. Methods

Details of syntheses, physical and analytical data on new compounds described in the thesis, and descriptions of NMR spectroscopic analyses of tautomeric equilibria can be found in the Experimental part of the enclosed publications.

4. SUMMARY

Chlorosulfonyl isocyanate addition to indene takes places regio- and stereoselectively, in accordance with the Markovnikov orientation rule, resulting in *cis*-*N*-chlorosulfonyl-3,4-benzo-6-azabicyclo[3.2.0]heptan-7one (**91**), which was hydrolysed with sodium sulfite to *β*-lactam **92**. Treatment of **92** with hydrochloric acid resulted in *cis*-1-aminoindane-2-carboxylic acid hydrochloride (**93**), while treatment with ethanolic hydrogen chloride led to ethyl ester **95**. Sodium ethoxide isomerization of **95**, followed by acidic hydrolysis, resulted in the *trans*-1-aminoindane-2-carboxylic acid hydrochloride (**96**). The free amino acids of **93** and **96** were liberated by ion-exchange chromatography. Starting from *β*-lactam **92**, the syntheses of all four enantiomers of 1-aminoindane-2-carboxylic acid **99** and **102-104** proved possible by a combination of lipase-catalysed *O*-acylation, hydrolysis and isomerization. The absolute configurations of the prepared amino acids were determined by X-ray investigation.

By means of highly regio- and diastereoselective functionalizations of *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acid derivatives, isomers of new hydroxy-substituted *β*-amino acids were prepared. *N*-Acyl derivatives of **106** and **114** were transformed to 1,3-oxazines **107, 110, 111** and **115** by using *N*-bromo- or *N*-iodosuccinimide. Selective reduction of the halogen group and subsequent hydrolysis led to the diastereomers of *all-cis*-2-amino-4-hydroxycyclohexanecarboxylic acid (**113**) and (*r*-1,*t*-2,*c*-4)-**116**. Iodolactonization of *N*-protected amino acids **124** and **128** resulted in γ-lactone intermediates **125** and **129**, which were transformed to regioisomeric *all-cis*-2-amino-5-hydroxycyclohexanecarboxylic acid (**127**) and (*r*-1,*t*-2,*c*-5)-**131** diastereomers via selective reduction and hydrolysis. The syntheses of enantiomers (+)-**113** and (-)-**127** were carried out similarly as for the racemic compounds. By the same method, the corresponding 3,5-*diendo*-2-*exo*-3-amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride (**121**) and *all-endo*-3-amino-6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride (**135**) were obtained from *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid derivatives **117** and **132**.

On melting of the norbornene- and norbornane-fused azetidinones **136a** and **136b**, and lactim ethers **137-140**, 1,4-methanopyrrolo-, 1,4-methanopyrido- and 1,4-methanoazepino[2,1-*b*]quinazolinones **141a,b-144a,b**, new ring systems, were prepared. The first step in the reaction is the formation of an amidine intermediate

which, after transamidation, results in the ring enlargement products **141a,b-144a,b**. Norbornene derivatives **141a-144a** underwent retrodiene decomposition to give pyrrolo-, pyrido- and azepino[1,2-*a*]pyrimidinones **145-148**, respectively. This is a new method for the synthesis of heterobicycles **145-148.**

Ethyl *cis*- and *trans*-2-isothiocyanato-1-cyclopentanecarboxylates (**152** and **157**) were prepared by the reactions of corresponding alicyclic ethyl 2-amino-1-carboxylates and thiophosgene. The *cis* isothiocyanate **152** underwent ring closure with amines, resulting in 3-substituted-*cis*-2-thioxo-cyclopenta[*d*]pyrimidin-4-ones **153a-g**. The *trans* isomer **155** failed to cyclize, but gave carboxamide **158a,b** or thiourea ester derivatives **159a,b**. The differences observed in the present study may serve as supporting evidence for the differences in the ring-closure reactivities of *cis*- and *trans*-1,2-disubstituted 1,3-difunctional cyclopentane derivatives.

By ring-closure reactions of *cis*-1-amino-2-hydroxymethylindane (**163**) and *cis*-1-benzylamino-2-hydroxymethylindane (**165**) with carbon disulfide, ethyl *p*-chlorobenzimidate, ethyl isothiocyanate/methyl iodide, ethyl isothiocyanate/hydrogen chloride, indano[1,2-*d*][1,3]oxazinone and thiazine, new ring systems were prepared. The reactions of *trans*-1-amino-2-hydroxymethylindane (**164**) with *p*-nitro-benzaldehyde gave Schiff base **175**, while the reactions of *N*-benzyl amino alcohol **165** with substituted benzaldehydes resulted in ring-closure products **176a-c** alone. The same reactions of *cis*-1-amino alcohol **163** led to 2-substituted-indano[1,2-*d*][1,3]oxazinones (**174a-g**), which at 300 K in $CDCl_3$ proved to be three-component tautomeric mixtures containing C-2 epimeric indanooxazines (**174Ca-g** > **174Ba-g**), besides the open tautomer (**174Aa-g**)

Racemic 1,2,3,4-tetrahydro-*β*-carboline-1-carboxylic acid (**177**) was esterified by refluxing in ethanol with thionyl chloride or reaction with dry hydrogen chloride gas in ethanol. The reactions of 1,2,3,4-tetrahydro-*β*-carboline-1-carboxylic acid (**177**) and its ester **178** with alkyl and aryl isothiocyanates under mild conditions resulted in the corresponding 2-substituted-5,6,11,11*b*-tetrahydro-1-oxo-1H-imidazo[1',5':1,2]-pyrido[3,4-*b*]indole-3-thiones (**180a-h**). Treatment of the ethyl ester with isocyanates furnished ethyl 2-alkyl- or arylcarbamoyl-1,2,3,4-tetrahydro-*β*-carboline-1-carboxylates (**181a,b**), which were transformed to **182a,b** hydantoin-fused tetrahydro-*β*-carbolines.

5. ACKNOWLEDGEMENTS

I am greatly indebted to Professor Gábor Bernáth, former Head of the Institute, for providing me with the opportunity to work at the Institute.

I would like to express my warmest thanks to Professor Ferenc Fülöp, present Head of the Institute, for his guidance of my work, his inspiring ideas, his useful advice and his constructive criticism.

I would like to thank Professor Pál Sohár, Dr. Tamás Martinek, Ferenc Evanics and Anasztázia Hetényi for helpful discussions concerning the NMR assignments.

I am grateful to Dr. David Durham for revising the English language of the thesis.

I owe very much to my colleagues, my friends and my family for creating all the circumstances enabling me to carry out this work.

Without their help, this thesis could not have been prepared.

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ANNEX

I.

SYNTHETIC COMMUNICATIONS, 27(2), 195-203 (1997)

SYNTHESIS AND MILD RETRO DIELS-ALDER DECOMPOSITION OF 1,4-METHANOPYRROLO-, 1,4-METHANOPYRIDO- AND 1,4-METHANOAZEPINO[2,1-*b*]QUINAZOLINONES[1]

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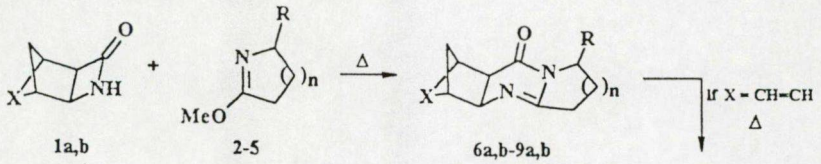
Abstract: From norbornane- and norbornene-fused azetidinones 1a and 1b, 1,4-methanopyrrolo-, 1,4-methanopyrido- and 1,4-methanoazepino[2,1-b]quinazolinones 6a,b-9a,b were prepared by ring enlargement. Norbornene derivatives 6b-9b underwent retrodiene decomposition to give pyrrolo-, pyrido- and azepino-[1,2-a]pyrimidinones 10-13, respectively.

Fused pyrimidinones are widely-used sources for the synthesis of new potential therapeutic agents.[2-6] The pyrrolo- and pyrido[2,1-*b*]quinazolines include well-known alkaloids isolated from a number of families of plants. *Adhatoda vasica* containing vasicine (peganine) has been used in Indian indigenous medicine for centuries. Because of their therapeutic interest, the syntheses of pyrido[2,1-*b*]-quinazolin-11-one derivatives and their ring A and C homologues have been studied very thoroughly.[4-6]

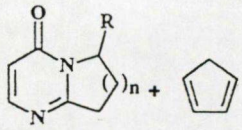
Although numerous papers deal with the synthesis of pyrido[2,1-*b*]quinazolin-11-ones and their differently saturated analogues and homologues,[6] the corresponding norbornane- and norbornene-fused derivatives **6-9** are not known.

In the first experiments for the synthesis of tetracycles **6-9**, 3-*exo*-amino-bicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid[7] or the corresponding saturated derivative or either of the ethyl esters was refluxed in chlorobenzene with 2 equivalents of lactim ethers **2-5**, as described for the synthesis of *cis*- and *trans*-



1a,b 2-5 6a,b-9a,b

No	n	R
2, 6, 10	1	H
3, 7, 11	1	Me
4, 8, 12	2	H
5, 9, 13	3	H



10-13

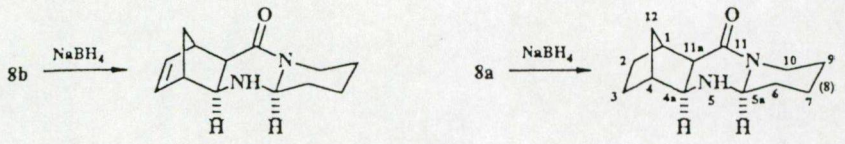
a: X = CH_2-CH_2; **b**: X = CH=CH

Scheme 1

decahydropyrido[2,1-*b*]quinazolin-11-one.[8] After refluxing for 24 hours, the starting materials were recovered unchanged. When azetidinones[7,9] **1a** and **1b** were reacted in chlorobenzene with lactim ethers, a very slow transformation was observed, and the reaction mixture turned deep-brown.

On melting of the azetidinones **1a** and **1b** with 2 equivalents of lactim ethers **2-5** at 80 °C for 8-10 hours, the desired tetracycles **6a,b-9a,b** were obtained. The first step of the reaction is the formation of an amidine intermediate which, after transamidation,[10,11] results in the ring enlargement products **6a,b-9a,b**. On increase of the temperature, the colour of the reaction mixture becomes deeper, and in the series **1b** the smell of cyclopentadiene is observed. Following melting of **1b** with **3** at 100 °C, 6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-one was isolated in low yield through the splitting-off of cyclopentadiene. Retrodiene decomposition under similarly mild conditions was described only recently for the synthesis of monocyclic 1,3-hetero derivatives.[12] The bicyclic hetero compounds pyrimido-[2,1-*b*]thiazin-6-one and thiazolo[3,2-*a*]pyrimidin-5-one have also been prepared by this method.[13]

In order to establish the scope and limitations of this mild retrodiene decomposition resulting in heterobicycles, tetracycles **6-9** were melted at 100 °C. When **6b-9b**



14 15

Scheme 2

were melted for 30 minutes, pyrrolo-, pyrido- and azepino[1,2-*a*]pyrimidinones **10-13** were formed in good yield by the splitting-off of cyclopentadiene. Starting from the series **6a-9a**, the formation of **10-13** could not be observed under similar conditions.

Because of their pharmacological interest,[14,15] a number of different synthetic routes have been devised for the synthesis of substituted analogues of **10-13**. Our method is a new, effective procedure for the preparation of the above derivatives.

Sodium borohydride reduction of **8b** resulted stereospecifically in the decahydro derivative **14** with relative configuration *r*-1,*c*-4,*c*-4a,*c*-5a,*c*-11a. When **8a** was reduced with sodium borohydride, the perhydro derivative **15** was formed. Their similar relative configurations were proved both spectroscopically and chemically: catalytic reduction of **14** gave a compound identical with the product of **15**. Attempted retrodiene decomposition was unsuccessful from both **14** and **15**. The successful and failed retro Diels-Alder reactions show that a retrodiene decomposition under mild conditions takes place only when the decomposition results in a heterocycle with a quasi-aromatic character through the splitting-off of cyclopentadiene.

The spectral data proving the expected structures of the newly synthesized compounds are given in Tables 1 and 2. They are self-explanatory. Only the following remarks are necessary.

The fact that the *diexo* annelation of the starting compounds remains unaltered in the products **6-9** and **12-15** is evidenced by the double split of the H-4a signal. For *diexo* isomers, a further split to a double doublet is characteristic.[17] The ring strain in **6a,b** and **7a,b** is manifested[16] in higher νC=O IR frequencies.

Table 1. Characteristic IR frequencies (cm^{-1}, in KBr) and ^{1}H-NMR data (chemical shifts in δ,δ_{TMS} = 0 ppm and coupling constants in Hz) in $CDCl_3$ solutions of compounds 6a,b-9a,b and 11-15 at 250.14 MHz[a]

Com-pound	Ir bands . νC=O	νC=N[b]	NCH_2(10)*m* (2H)[c]		CH(1) ~*s*(1H)	CH(4) ~*s*(1H)	CH(4a) *d*(1H)[d]	CH(11a) *d*(1H)
6a	1710	1664	3.71		2.65[e]	2.43[f]	3.79	2.40[f]
6b	1706	1670	3.75[e]		3.30	3.10	3.75[e]	2.30
7a[g]	1711	1679	4.38		2.35-2.8[e]		3.78	2.35-2.8[e]
7b	1710	1666	4.42		3.31	3.09	3.73[h]	2.30
8a		1674	~3.65[e]		2.66	2.43	3.68[e]	~2.5
8b		1666	~3.7[e]		2.29	3.11	3.62[e]	2.38
9a		1664	3.72[e]	4.00	2.67	2.44[f]	3.69[e]	2.46[f]
9b		1667	3.80	4.02	3.28	3.11	3.62	2.33
10	1658	1588	4.16		-	-	7.86	6.28
11	1685	1597	4.82		-	-	7.84	6.27
12	1667	1514	3.97		-	-	7.82	6.32
13	1680	1658	4.32		-	-	7.74	6.32
14	1620	3297	2.65	4.52	3.44	2.81	3.12	2.00
15	1622	3293	2.60	4.51	2.90	2.21	3.17	2.11

[a]For easier comparison of spectroscopically analogous data, the numbering of 15 (see Scheme 2) were used in the text and Tables. The IUPAC numbering is given in the Experimental. Assignments were proved by 2D-HSC (6a,b, 7b, 8a, 9a,b, 14, 15), DNOE (6b, 7b, 9b, 14, 15) and DR (6b) experiments. Further signals: CH_3(10), *d* (*J*: 6.5): 1.26 and 1.28 (7a[i]), 1.31 (7b), 1.45 (11); H-2,3(*endo*), *m* (2H): ~1.6 (6a, 7a, 8a, 9a[e], 15); H-2,3(*exo*) + H-12(*endo*), *m* (3H): 1.25-1.5 (6a, 7a, 8a, 9a, 15); olefinic H-2,3 in 6b, 7b, 8b, 9b and 14, 2x*dd* (*J*: 5.7±0.1 and 3.0±0.1): 6.20 and 6.30, for 15: 6.09 and 6.31 (2x1H); H-5a, *dd* (*J*: 10.3 and 3.8): 4.08 (14), 4.01 (15); CH_2(6), *m*(2H): 2.6±0.5 for 6a,b, 8a,b and 9a,b (in overlap with the H-1 *m* for 6a), 3.14 (10), 2.93 (12), 3.0 (13), 2x*m* (2x1H): 2.60 and 2.78 (7a,b in overlap with the H-1,4,11a *m*'s for 7a), 3.03 and 3.20 (11), 1.2 and 2.0 (14, 15), CH_2(7-9), *m*: 1.8-2.05 (2H for 6a,b and 10, 4H for 8a,b and 12, 6H for 13), 1.5-1.9 (6H for 9a,[c]4H for 14 and 15), 2x*m* (2x1H): 1.65 and 2.05 (7a,b), 2.26 (11), 1.9 and 2.4 (11); H-12(*exo*), *td* (1H): 1.18±0.02 (6a, 7a, 8a, 9a, 15); CH_2(12), 2x*d* (*J*: 9, further *t* split of one of the *d*'s by <1 Hz, due to long-range couplings): 1.32±0.02 (in overlap with *d* of CH_3 for 7b) and 1.42±0.02 (for 6b, 7b, 8b and 9b), 1.40 and 1.62 (14); [b]νNH band for 14, 15; [c]NCH(1H) for 7a,b and 11, multiplicity: *dt* (*J*: 7.5 and 1.0, 6a), *dqi* (1H) for 2a,b, unresolved *m* for 8b, 11 and 13, 2x*dd* for 9a,b (*J*: 15.2, 7.8 and 14.5, 7.0) for 14 and 15: *dt* (*J*: 10, 10, 3.5 and 12, 12, 5) and *dd* (12.2, 2.7 in both cases), *t* for 12 (*J*: 6.0); [d]*J*: 8.7 (6a,b-9a,b), 6.7 (10-13), 7.5 (14, 15); [e,f]Overlapping signals; [g]1:1 Mixture of C-10 diastereomers; [h]Further split by 1 Hz to *dd*; [i]Doubled signal due to diastereomers.

Table 2. ^{13}C-nmr chemical shifts (δ_{TMS} = 0 ppm) for compounds 6a,b-9a,b and 11-15 in $CDCl_3$ solution at 62.89 MHz[a]

Com-pound	CH (1)	C-2[b]	C-3[b]	CH(4)	CH[c] (4a)	C-5a[d]	CH_2 (6)	CH_2 (7)	CH_2 (8)	CH_2 (9)	NCH_2[e] (10)	CH[c] (11a)	CH_2 (12)	C=O (11)
6a	42.4	29.4	25.6	45.4	65.3	154.3	31.3		18.3		44.1	46.1	34.0	168.4
6b	48.4	139.0	136.2	52.8	62.1	155.5	31.4		18.9		44.3	41.6	44.1	168.7
7a[f]	42.4	29.6[g]	26.0[h]	45.6	65.2	154.6	29.7[g]		26.1[h]		52.3	47.1	34.0	168.3
	43.1			45.9	65.4				26.2h		52.5	47.2	34.2	
7b	48.1	139.0	136.1	51.9	62.0	155.2	29.4		26.7		52.5	42.0	44.2	168.1
8a	43.9	30.2	26.6	46.5	62.9	150.2	32.1		19.9 22.7		40.6	48.3	34.7	169.6
8b	49.1	138.8	136.1	52.4	58.5	150.6	31.7		19.2 22.1		40.2	42.1	43.9	169.9
9a	43.4	29.6	26.0	46.0	62.5	154.6	37.1		28.6[g] 26.2 29.4[g]		41.2	47.0	34.0	169.6
9b	49.2	138.9	136.2	52.2	58.6	155.0	37.2		28.7[g] 26.1 29.4[g]		41.3[i]	41.3[i]	43.7	169.9
10	-	-	-	-	154.0	161.2	32.4		18.5		46.7	112.5	-	164.7
11	-	-	-	-	154.0	~160	31.1		26.9		56.1	113.3	-	164.4
12	-	-	-	-	152.5	160.4	31.4		18.9 21.6		42.3	112.2	-	162.3
13	-	-	-	-	152.3	162.0	37.2		27.1[g] 24.5 29.4[g]		42.4	112.9	-	165.2
14	45.4	139.2	134.6	48.1	54.5	67.1	33.5		22.1 24.2		40.7	44.5	43.7	172.0
15	40.2	29.1	26.0	42.8	59.0	66.4	33.6		22.1 24.3		40.7	50.0	34.3	171.5

[a]For easier comparison of analogous spectral data the numbering of 15 was used for all compounds investigated. Assignments were proved by DEPT (except for 10, 12 and 13) and 2D-HSC measurements (except for 7a, 10, 12 and 13). Further signals: CH_3: 18.9 and 19.0 (7a), 19.0 (7b, 11). [b]CH_2 group for 6a-9a and 15, olefinic CH group for 6b-9b and 14; [c]Methine sp^3 (sp^2 for 10-13) carbon vicinal to the nitrogen (Pos. 4a) or the carbonyl (Pos. 11a); [d]N=C-N-type quaternary carbon or N-CH-N group (14, 15); [e]NCH group for 7a,b and 11; [f]1:1 Mixture of C-10 diastereomers; [g,h]Interchangeable assignments; [i]Two overlapping lines.

Compounds **7a,b** may exist in two diastereomeric forms differing in the C-10 configurations. The NMR data suggest an approximately 1:1 mixture of such isomers for **7a**, but a stereohomogeneous sample for **7b**.

The free pseudorotation of the pyrroline ring results in the differences in the spectral data on the isomers being very small (hardly significant) for all the ^{13}C-NMR shifts, *e.g.* <0.3 ppm.

The all-*cis* configuration of H-4a,5a,11a in **14** and **15** was proved by DNOE measurements.[18,19] On saturation of one of these signals, intensity enhancements for both of the others were observed, confirming their steric proximity. These experiments, together with 2D-HSC[20] results, allow the firm assignment of close-lying signals in the ^{1}H and ^{13}C-NMR spectra, *e.g.* the H-1,4 and C-1,4 singlet pairs or the *exo* and *endo* H-12 doublets.

EXPERIMENTAL

The IR spectra were measured in KBr pellets on an Aspect 2000 computer-controlled Bruker IFS-113v vacuum optic FT spectrometer.

The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5-mm tubes at room temperature on a Bruker WM-250 FT spectrometer at 250.13 (^{1}H) and 62.89 MHz (^{13}C), respectively, using the ^{2}H signal of the solvent as the lock and TMS as internal standard. NOE difference (DNOE) and two-dimensional heteronuclear shift correlation (2D HSC) measurements were carried out with the standard software written for the Aspect 2000 computer of the Bruker spectrometers. DEPT spectra[21] were run in a standard way,[22] using only the Θ = 135° pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively.

Pyrrolo-, Pyrido- and Azepino[2,1-*b*]quinazolinones (6a,b-9a,b); General Procedure:

A mixture of the azetidinone **1a** or **1b** (3.6 mmol) and the corresponding lactim ether (7.2 mmol) was kept at 100-110 °C for 8 hours. The excess of the lactim ether was evaporated off and the residue was dissolved in diethyl ether (20 ml), treated with charcoal, filtered and left to stand at 4 °C. The product **6a,b-9a,b** that separated out was filtered off (yields: 70-80%) and recrystallized.

Table 3. Analytical data on compounds 6a,b-9a,b and 10-15

No	Mp °C Solvent	Formula Mw	Analysis (%) C Calcd./Found.	H Calcd./Found.	N Calcd./Found.
6a	101-103	$C_{12}H_{16}N_2O$	70.56	7.90	13.71
	iPr_2O	204.28	70.58	8.32	13.72
6b	122-124	$C_{12}H_{14}N_2O$	71.26	6.98	13.85
	iPr_2O	202.26	70.94	6.33	13.59
7a[a]	152-160	$C_{13}H_{19}ClN_2O$	61.29	7.52	11.00
	EtOH/Et_2O	254.76	60.89	7.66	11.09
7b	130-136	$C_{13}H_{16}N_2O$	72.19	7.46	12.95
	iPr_2O	216.29	71.26	7.94	12.96
8a	36-40	$C_{13}H_{18}N_2O$	71.53	8.31	12.83
	Et_2O	218.30	71.78	8.40	12.77
8b	105-106	$C_{13}H_{16}N_2O$	72.19	7.46	12.95
	iPr_2O	216.29	70.68	7.98	13.95
9a	98-99	$C_{14}H_{20}N_2O$	72.38	8.68	12.06
	iPr_2O	232.33	71.42	8.83	12.72
9b	118-120	$C_{14}H_{18}N_2O$	73.01	7.88	12.16
	iPr_2O	230.31	73.03	8.26	12.64
10	104[b]	$C_7H_8N_2O$	61.75	5.92	20.57
	hexane	136.16	60.98	5.88	20.79
11[a]	177-179	$C_8H_{11}ClN_2O$	51.48	5.94	15.01
	EtOH/Et_2O	186.64	51.06	6.18	15.49
12	84-86	$C_8H_{10}N_2O$	63.98	6.71	18.65
	hexane	150.18	63.54	6.82	18.39
13	62-63[c]	$C_9H_{12}N_2O$	65.83	7.37	17.06
	hexane	164.21	65.39	7.58	17.11
14	133-135	$C_{13}H_{18}N_2O$	71.53	8.31	12.83
	hexane	218.30	71.84	8.55	12.61
15	142-144	$C_{13}H_{20}N_2O$	70.87	9.15	12.71
	hexane	220.32	70.47	9.43	12.74

[a]Hydrochloride. [b]Lit.[9] mp 101 °C. [c]Lit.[9] mp 66-67 °C.

Pyrrolo-, Pyrido- and Azepino[1,2-*a*]pyrimidinones (10-13); General Procedure:

The tetracycles **6b-9b** (1 mmol) were heated at about 110-130 °C for 20 minutes. The crude product was dissolved in diethyl ether (20 ml), and the solution was treated with charcoal, filtered and evaporated. The products were recrystallized from hexane, yields: 70-80%.

(*r*-1,*c*-4,*c*-4a,*c*-5a,*c*-11a)-1,4-Methano-1,4,4a,5,5a,6,7,8,9,11a-decahydro-pyrido[2,1-*b*]quinazolin-11-one (14)

To a methanolic (10 ml) solution of **8b** (1 mmol), sodium borohydride (2 mmol, 76 mg) in water (10 ml) was added dropwise with stirring at room temperatute. After stirring for 2 hours, the methanol was evaporated off, and the aqueous phase was extracted with diethyl ether (3x20 ml). The combined organic extrcts were dried (Na_2SO_4), and the solvent was evaporated off. The residue crystallized on treatment with diethyl ether and was recrystallized from hexane, yield: 86%.

(*r*-1,*c*-4,*c*-4a,*c*-5a,*c*-11a)-1,4-Methano-1,2,3,4,4a,5,5a,6,7,8,9,11a-dodecahydro-pyrido[2,1-*b*]quinazolin-11-one (15)

The reaction was performed similarly as for **14**, starting from **8a**, yield: 79%.

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(Received in The Netherlands 16 July 1996)

II.

Synthesis and Transformations of Stereoisomeric Ethyl 2-Isothiocyanato-1-cyclopentanecarboxylates

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Received November 1, 1999

Dedicated to the memory of Raymond N. Castle

Ethyl *cis*- and *trans*-2-isothiocyanato-1-cyclopentanecarboxylates **2** and **7** were prepared by the reaction of the corresponding alicyclic ethyl 2-amino-1-carboxylates and thiophosgene. The *cis*-isothiocyanato compound **2** underwent ring closure with amines in one or two steps, resulting in 3-substituted-*cis*-2-thioxocyclopenta[*d*]pyrimidin-4-ones **3a-g**. The *trans* isomer **7** failed to cyclize, but gave carboxamide **8a,b** or thiourea ester derivatives **9a,b**.

J. Heterocyclic Chem., **37**, 779 (2000).

Introduction

Although six-membered saturated 1,3-heterocycles and their benzene ring-fused derivatives have been studied thoroughly, much less attention has been paid to the bicyclic saturated derivatives. The synthesis and conformational study of saturated or partially saturated six-membered 1,3-heterocycles *cis*- or *trans*-fused with 5-, 6-, 7- or 8-membered alicycles has therefore been one of our main research topics [1].

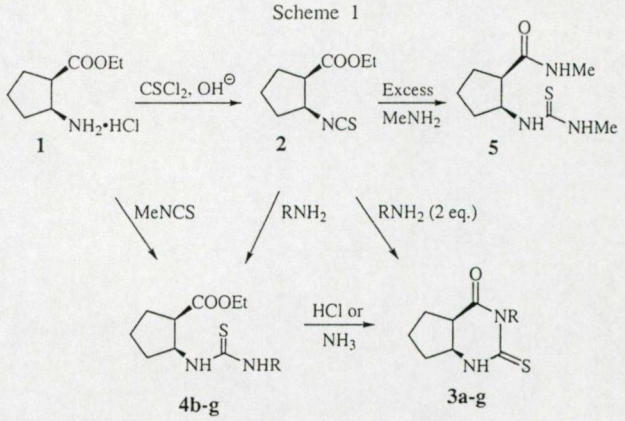
Isocyanato [2] and isothiocyanato compounds [3,4] are widely used for the preparation of ureas, thioureas and heterocyclic derivatives [5], which have a wide range of biological activities. Some of the isothiocyanato compounds have also found applications in the synthesis of agrichemicals and pharmaceuticals [6]. They are particularly valuable building blocks for the synthesis of different heterocycles [2,7-10]. Isothiocyanato compounds have mainly been prepared by the reactions of amines with thiocarbonyl reagents such as carbon disulfide or thiophosgene [11].

Results and Discussion

This paper describes the preparation of ethyl *cis*- and *trans*-2-isothiocyanato-1-cyclopentanecarboxylates **2** and **7**, from the corresponding ethyl 2-amino-1-cyclopentanecarboxylates **1** and **6** with thiophosgene (Schemes 1 and 2).

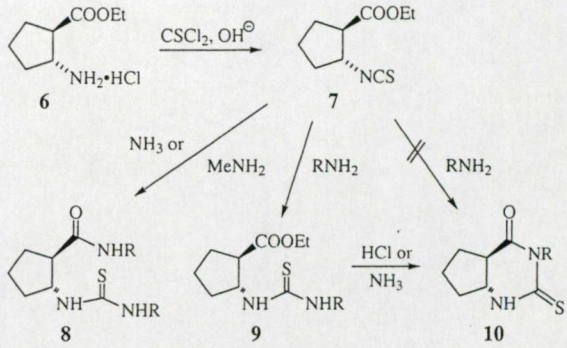
cis-2-Amino-1-cyclopentanecarboxylic acid was prepared from cyclopentene by addition of chlorosulfonyl isocyanate and subsequent ring opening of the resulting azetidinone with hydrochloric acid [12]. The *trans* isomer was obtained by the addition of ammonia to 1-cyclopentene-1-carboxylic acid [13]. The amino acids were transformed to the amino ester hydrochlorides **1** [14] and **6** [15] with thionyl chloride and ethanol. Isothiocyanato compounds **2** and **7** can be prepared through reaction of the ester hydrochlorides **1** or **6** with thiophosgene in the presence of sodium hydrogencarbonate at 40°C and subsequent column chromatography of the crude oily products.

Scheme 1



R = H: **a**; R = Me: **b**; R = *i*-Pr: **c**; R = Ph: **d**; R = CH_2Ph: **e**; R = CH_2CH_2Ph: **f**; *p*-tolyl: **g**

Scheme 2



R = H: **a** R = Me: **b** R = Ph: **a** R = *p*-tolyl: **b**

It is interesting that the chemical shifts of **6** and **7** happen to be practically the same, probably because of the magnitudes of the electronic and anisotropic effects of the 2-substituent. The difference in the multiplicity of 2-H is caused by the steric difference between NH_2

Table 1

Physical and Analytical Data for Compounds 2-9

Compound	Yield (%)	Method	Mp (°C)	Formula (Mw)	Calcd Found C (%)	H (%)	N (%)
3a	62	B	200-203	$C_7H_{10}N_2OS$	49.39	5.92	16.46
			[a] [b]	(170.24)	49.02	6.28	16.64
3b	60	C	132-135	$C_8H_{12}N_2OS$	52.15	6.56	15.20
	55	D	[c] [d]	(184.26)	51.98	6.61	15.10
	65	E					
3c	63	E	131-133	$C_{10}H_{16}N_2OS$	54.90	7.15	7.64
			[c]	(222.40)	54.55	7.25	7.99
3d	69	E	282-284	$C_{13}H_{14}N_2OS$	63.39	5.73	11.37
			[c] [e]	(246.33)	63.11	5.67	11.05
3e	67	E	162-165	$C_{14}H_{16}N_2OS$	64.59	6.19	10.76
			[f]	(260.36)	64.29	6.43	10.93
3f	75	E	136-137	$C_{15}H_{18}N_2OS$	65.66	6.61	10.21
			[g]	(274.39)	65.35	6.84	10.47
3g	78	E	292-294	$C_{14}H_{16}N_2OS$	64.59	6.19	10.76
			[h]	(260.36)	64.30	6.28	10.54
4c	77	F	67-68	$C_{12}H_{22}N_2O_2S$	55.78	8.58	10.84
			[g]	(258.39)	55.92	8.70	10.61
4d	69	F	61-64	$C_{15}H_{20}N_2O_2S$	61.62	6.89	9.58
			[g] [i]	(292.40)	61.87	6.96	9.39
4e	83	F	80-82	$C_{16}H_{22}N_2O_2S$	62.72	7.24	9.14
			[j]	(306.43)	62.93	7.60	9.50
4g	72	F	64-68	$C_{16}H_{22}N_2O_2S$	62.72	7.24	9.14
			[j]	(306.43)	62.78	7.48	8.92
5	74	G	100-104	$C_9H_{17}N_3OS$	50.20	7.96	19.52
			[g]	(215.32)	50.33	8.09	19.36
8a	60	G	154-157	$C_7H_{13}N_3OS$	44.90	7.00	22.44
			[c]	(187.27)	45.02	7.29	22.78
8b	61	G	132-138	$C_9H_{17}N_3OS$	50.20	7.96	19.52
			[c]	(215.32)	50.36	8.12	19.22
9a	78	F	78-80	$C_{15}H_{20}N_2O_2S$	61.62	6.89	9.58
			[c] [k]	(292.40)	61.35	6.99	9.31
9b	82	F	102-105	$C_{16}H_{22}N_2O_2S$	62.72	7.24	9.14
			[c]	(306.43)	63.05	7.53	9.12

[a] From ethyl acetate. [b] Lit. mp [14]: 205-208°C. [c] From diethyl ether/methanol. [d] Lit. mp [16]: 134-137°C. [e] Lit. mp [16]: 285-287°C. [f] From ethyl acetate/diethyl ether. [g] From diethyl ether/diisopropyl ether. [h] From dimethylformamide. [i] Lit. mp [16]: 66-69°C. [j] From diisopropyl ether. [k] Lit. mp [16]: 70-73°C.

and NCS, which could alter the geometry of the cyclopentane ring.

Isothiocyanates **2** or **7** were reacted with different amines and, depending on the reagent, the ratio of the reactants and the configuration of the isothiocyanate, three different products were formed. The *cis* **2** with two equivalents of ammonia or methylamine gave the corresponding *cis*-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidin-4-ones **3a** and **3b**, respectively. When an excess of ammonia was used, the product was again **3a**, but with an excess of methylamine, the *cis* **2** gave the thiourea **5**, the ester function was amidated rather than ring closure occurring.

Reactions of substituted amines such as isopropylamine, benzylamine, phenylethylamine, aniline and *p*-toluidine with **2** resulted in the corresponding thioureas **4c-g**. Thiourea **4b** was prepared from **1** with methyl isothiocyanate as described earlier [16]. Thioureas **4** can readily be cyclized using either acid (HCl) or base (*e.g.* NH_3) catalysts.

When the *trans* **7** (Scheme 2) was reacted with amines, the formation of the pyrimidinone **10** was not observed, even under forced conditions. But the reaction with ammonia or methylamine, leads to the thiourea-amide derivatives **8a** and **8b**. With aniline or *p*-toluidine, the *trans* thioureas **9a** and **9b** were formed in good yields. The cyclization of *trans* thioureas **9a** and **9b** failed under both acidic and basic conditions.

It is noteworthy that in the ring closures of the 1,2-disubstituted-1,3-difunctional cyclohexane, cycloheptane and cyclooctane derivatives, no appreciable differences were found in the reactivities of the *cis* and *trans* isomers in the formation of six-membered 1,3-heterocycles fused with carbocycles [1,17]. In contrast, very striking differences were observed in the cyclization reactivities of the *cis*- and *trans*-1,2-disubstituted 1,3-difunctional cyclopentane derivatives, such as 2-hydroxymethyl-1-cyclanols and alicyclic 2-aminomethyl-1-amines, or in the cases of *cis*- and *trans*-2-hydroxy-1-cyclopentanecarboxamides or *cis*- and *trans*-2-amino-1-cyclopen-

Table 2

^{1}H-NMR Parameters of Compounds **2-9**

Compounds	^{1}H NMR data
2	4.35 m, 1 H (1); 4.30-4.16 m, 2 H (CH_2CH_3); 2.92 m, 1 H (2); 2.16 m, 1 H; 2.07-1.90 m, 4 H; 1.75 m, 1 H; 1.32 t, 3 H, J= 7.1 (CH_2CH_3)
3a	8.38 brs, 1 H (NH); 7.13 brs, 1 H (NH); 4.08 m, 1 H (7a); 2.88 m, 1 H (4a); 2.23 m, 1 H; 2.11-1.99 m, 2 H; 1.95-1.72 m, 3 H
3b	7.83 brs, 1 H (NH); 4.00 m, 1 H (7a); 3.56 s, 3 H (NCH_3); 2.95 m, 1 H (4a); 2.22 m, 1 H; 2.07-1.86 m, 4 H; 1.75 m, 1 H
3c	7.16 brs, 1 H (NH); 5.70 sep, 1 H, J= 6.8 ($CH(CH_3)_2$); 3.95 m, 1 H (7a); 2.85 m, 1 H (4a); 2.20 m, 1 H; 2.02-1.71 m, 5 H; 1.47 d, 3 H, J= 6.8 ($CH(CH_3)_2$); 1.42 d, 3 H, J= 6.8 ($CH(CH_3)_2$.)
3d	9.82 brs, 1 H (NH); 7.39-7.38 m, 2 H (Ar); 7.33-7.31 m, 1 H (Ar); 7.20-7.05 m, 2 H (Ar); 4.05 m, 1 H (7a); 3.05 m, 1 H (4a); 2.11 m, 1 H; 1.98 m, 2 H; 1.85 m, 1 H; 1.72 m, 2 H
3e	7.39 d, 2 H, J= 7.3 (Ar); 7.35 brs, 1 H (NH); 7.32-7.21 m, 3 H (Ar); 5.55 d, 1 H, J= 14.6 ($PhCH_2$); 5.49 d, 1 H, J= 14.6 ($PhCH_2$); 3.97 m, 1 H (7a); 2.94 m, 1 H (4a); 2.18 m, 1 H; 2.08-1.70 m, 5 H
3f	7.53 brs, 1 H (NH); 7.34-7.27 m, 4 H (Ar); 7.24-7.21 m, 1 H (Ar); 4.53-4.39 m, 2 H ($ArCH_2$); 3.95 m, 1 H (7a); 3.05-2.85 m, 3 H (NCH_2, 4a); 2.18 m, 1 H; 2.01-1.70 m, 5 H
3g	7.26-7.24 m, 2 H (Ar); 7.13 brs, 1 H (NH); 7.04-7.03 m, 2 H (Ar); 4.16-4.15 m, 1 H (7a); 3.06 m, 1 H (4a); 2.39 s, 3 H ($ArCH_3$); 2.32 m, 1 H; 2.18 m, 1 H; 2.09-1.80 m, 4 H
4b	6.64 brs, 1 H (NH); 6.01 brs, 1H (NH); 4.87 m, 1H (2); 4.10-4.17 m, 2H (CH_2CH_3); 3.10-3.05 dd, 1H, J= 7.64, 14.4 (1); 2.92, d, 3H, J= 4.8 (NCH_3); 2.16-2.13 m, 1H; 2.00-1.9 m, 2H; 1.82-1.61 m, 3H; 1.38-1.25 t, 3H, J= 7.64, 14.4 (CH_2CH_3)
4c	6.59 d, 1 H, J= 4.3 (NH); 5.83 d, 1 H, J= 5.8 (NH); 4.88 m, 1 H (2); 4.20-4.08 m, 2 H (CH_2CH_3); 3.9 m, 1 H; 3.08 m, 1 H (1); 2.19-1.93 m, 3 H; 1.86-1.61 m, 3 H; 1.27 t, 3 H, J= 7.1 (CH_2CH_3); 1.23 d, 3 H, J= 6.7 ($CH(CH_3)_2$); 1.21 d, 3 H, J= 6.7 ($CH(CH_3)_2$)
4d	8.01 brs, 1 H (NH); 7.44-7.39 m, 2 H (Ar); 7.30-7.27 m, 1 H (Ar); 7.20-7.17 m, 2 H (Ar); 6.93 d, 1 H, J= 7.8 (NH); 5.01 m, 1 H (1); 4.03 q, 2 H, J= 7.1 (CH_2CH_3); 3.10 m, 1 H (2); 2.13 m, 1 H; 2.04-1.85 m, 2 H; 1.80-1.59 m, 3 H; 1.17 t, 3 H, J= 7.1 (CH_2CH_3)
4e	7.37-7.29 m, 5 H (Ar); 6.63 d, 1 H, J= 8.1 (NH); 6.33 brs, 1 H (NH); 4.85 m, 1 H (1); 4.52 brs, 2 H ($PhCH_2$); 4.13-4.00 m, 2 H (CH_2CH_3); 3.03 m, 1 H (2); 2.10-1.85 m, 3 H; 1.74-1.57 m, 3 H; 1.24 t, 3 H, J= 7.2 (CH_2CH_3)
4f	7.34-7.29 m, 2 H (Ar); 7.26-7.21 m, 3 H (Ar); 6.61 brs, 1 H (NH); 5.98 brs, 1 H (NH); 4.80 m, 1 H (2); 4.17-4.05 m, 2 H (CH_2CH_3); 3.67-3.53 m, 2 H; 3.04 m, 1H (1); 2.89 m, 2 H; 2.13-1.92 m, 3 H; 1.84-1.59 m, 3 H; 1.25 t, 3 H, J= 7.1 (CH_2CH_3)
4g	8.17 brs, 1 H (NH); 7.23-7.20 d, 2 H, J= 8.3 (Ar); 7.09-7.07 d, 2 H, J= 8.3 (Ar); 6.82 d, 1 H, J= 9.1 (NH); 5.01 m, 1 H (1); 4.03 q, 2 H, J= 7.1 (CH_2CH_3); 3.10 m, 1 H (2); 2.35 s, 3 H (Ar-Me); 2.10 m, 1 H; 2.02-1.85 m, 2 H; 1.79-1.58 m, 3 H; 1.18 t, 3 H, J= 7.1 (CH_2CH_3)
5	7.62-7.23 brs, 1 H (NH); 7.14-7.03 brs, 1 H (NH); 6.52-6.36 brs, 1 H (NH); 4.87 m, 1 H (1); 3.18 m, 1 H (2); 3.02 d, 3 H, J= 3.5 (NCH_3); 2.70 d, 3 H, J= 4.8 (NCH_3); 2.10-1.89 m, 3 H; 1.83 m, 1 H; 1.66-1.50 m, 2 H
6	4.30 dt, 1 H, J= 6.5, 6.5 (1); 4.18 q, 2 H, J= 7.3 (CH_2CH_3); 2.93 m, 1 H (2); 2.19-2.07 m, 2H; 1.92-1.70 m, 4 H; 1.25 t, 3 H, J= 7.3 (CH_2CH_3)
7	4.30 dd, 1 H, J= 12.6, 6.3 (1); 4.18 q, 2 H, J= 7.0 (CH_2CH_3); 2.93 m, 1 H (2); 2.19-2.07 m, 2 H; 1.93-1.73 m, 4 H; 1.29 t, 3 H, J= 7.0 (CH_2CH_3)
8a	7.53 d, 1H, J= 7.4 (NH); 7.20-6.70 m, 4H (NH_2, NH_2); 3.20 m, 1H (2); 2.54 m, 1H (1); 1.98 m, 1H; 1.88 m, 1H; 1.65-1.55 m, 3H; 1.45 m, 1H
8b	7.7 brs, 1 H (NH); 6.4 brs, 1 H (NH); 4.4 brs, 1 H (NH); 3.07 d, 3 H, J= 4.3 (NCH_3); 2.82 d, 3 H, J= 4.8 (NCH_3); 2.62 m, 1 H (1); 2.18-1.98 m, 2 H; 1.85-1.70 m, 3 H; 1.60 m, 1 H
9a	7.4 m, 2 H (Ar); 7.35-7.22 m, 3 H (Ar); 6.2 brs, 1 H (NH); 4.8 brs, 1 H (NH); 4.19 q, 2 H, J = 7.1 (CH_2CH_3); 2.66 m, 1 H (2); 2.31 m, 1 H (1); 2.06-1.87 m, 2 H; 1.79-1.66 m, 2 H; 1.55-1.44 m, 2 H; 1.28 t, 3 H, J= 7.1 (CH_2CH_3)
9b	7.25-7.10 m, 4 H (Ar); 6.0 brs, 1 H (NH); 4.8 brs, 1 H (NH); 4.19 q, 2 H, J= 7.1 (CH_2CH_3); 2.63 m, 1 H (1); 2.36 s, 3 H ($ArCH_3$); 2.32 m, 1 H (2); 2.04-1.88 m, 2 H; 1.80-1.64 m, 2 H; 1.46 m, 1 H; 1.28 t, 3 H, J= 7.1 (CH_2CH_3)

tanecarboxylic acids [1]. The *cis* isomers react readily, while their *trans* counterparts do not undergo ring closure in most cases [1].

The difference observed in the present study may serve as supporting evidence for the difference in the ring closure reactivities of *cis* and *trans*-1,2-disubstituted-1,3-difunctional cyclopentane derivatives [1].

EXPERIMENTAL

The ^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution in 5 mm tubes at room temperature at 400.13 MHz on a Bruker AVANCE DRX 400 spectrometer, using the ^{2}H signal of the solvent as the lock and TMS as internal standard. Melting points were determined with a Kofler apparatus and the values are not corrected. The physical and analytical data on the compounds prepared are listed in Table 1. The ethyl *cis*- and *trans*-2-amino-1-cyclopentanecarboxylates **1** and **6** and the thiourea **4b** were prepared according to literature methods [12-16].

Preparation of Isothiocyanato Compounds **2** and **7** (Method A).

To a stirred mixture of chloroform (150 ml), water (80 ml), thiophosgene (5.75 g, 0.05 mol) and sodium hydrogencarbonate (12.6 g, 0.15 mol), a solution of ethyl *cis*- or *trans*-2-amino-1-cyclopentanecarboxylate hydrochloride **1** or **6** (0.05 mol) in water (80 ml) was added dropwise during a period of 40 minutes (Caution: thiophosgene is volatile and highly toxic - use hood.) After stirring for 3 hours at 40°C, the chloroform layer was separated and dried over magnesium sulfate. It was diluted with *n*-hexane (400 ml), and purified by passing through a silica gel

passing through a silica gel column. The ^{1}H-NMR spectra indicated that the oily isothiocyanato compounds **2** and **7** obtained had a purity > 96% (Table 2).

cis-2-Thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]-pyrimidin-4-one **3a** (Method B).

To a methanolic solution of isothiocyanate **2** (398 mg, 2 mmol in 10 ml), two equivalents of ammonia (25%, 0.3 ml) in methanol was added and the mixture was left to stand at ambient temperature overnight. After evaporation to dryness, the solid residue **3a** was recrystallized.

cis-3-Methyl-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]-pyrimidin-4-one (**3b**) (Method C).

To a methanolic (absolute) solution of isothiocyanate **2** (398 mg, 2 mmol in 10 ml), two equivalents of methylamine (40%, 0.35 ml) in methanol was added and the mixture was left to stand at ambient temperature overnight. After evaporation to dryness, the solid residue **3b** was recrystallized.

cis-3-Methyl-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta-[*d*]pyrimidin-4-one **3b** (Method D).

The thiourea derivative **4b** (253 mg, 1.1 mmol) was dissolved in absolute methanol (15 ml), and ammonia (25%, 0.2 ml) in methanol was added dropwise. The mixture was left to stand at ambient temperature overnight. The solvent was evaporated, diethyl ether (5 ml) was added to the oily residue and the precipitate was collected by filtration to give **3b**.

cis-3-Methyl-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta-[*d*]pyrimidin-4-one **3b** (Method E).

The thiourea derivative **4b** (2 mmol) was dissolved in hydrochloric acid (10%, 15 ml) and the solution was refluxed for 12 hours. After keeping for overnight, the crystalline product obtained was separated by filtration and recrystallized. Compounds **3c-g** were prepared as above.

N-Isopropyl-*N'*-(2-ethoxycarbonylcyclopentyl)thiourea **4c** (Method F).

Isothiocyanato compound **2** (398 mg, 2 mmol) was dissolved in methanol (15 ml), and the equivalent amount isopropylamine in methanol (10 ml) was added. The mixture was left to stand overnight at ambient temperature. After evaporation to dryness, the solid residue was recrystallized. Compounds **4d-g** and **9a,b** were prepared as above. The oily product **4f** was purified by column chromatography (toluene:methanol = 19:1)

N-Methyl-*N'*-(2-methylaminocarbonylcyclopentyl)thiourea **5** (Method G).

Isothiocyanate **2** (398 mg, 2 mmol) was dissolved in absolute methanol (15 ml), and an excess of methylamine (40%, 10 ml) in methanol was added dropwise. The mixture was left to stand overnight at ambient temperature. After evaporation to dryness, the solid residue was recrystallized. Compounds **8a,b** were prepared as above.

Acknowledgement

This work was supported by the National Scientific Research Foundation, Hungary (Grants OTKA T 020454 and T 030647).

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III.

Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4179–4187

TETRAHEDRON: *ASYMMETRY*

Synthesis of all four enantiomers of 1-aminoindane-2-carboxylic acid, a new cispentacin benzologue

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Received 5 September 2000; accepted 15 September 2000

Abstract

Racemic *cis*- and *trans*-1-aminoindane-2-carboxylic acids (**3** and **5**) were prepared from indene by chlorosulphonyl isocyanate addition followed by ring opening and isomerisation. The intermediate racemic hydroxymethylated β-lactam **6** was resolved through the lipase-catalysed asymmetric acylation of the primary hydroxy group at the (*R*)-stereogenic centre. High enantioselectivities ($E>200$) were observed when the enzymatic reactions were performed with lipase AK or lipase PS as catalyst and vinyl acetate or vinyl butyrate as acyl donor. The hydrolysis and isomerisation resulted in all four enantiomers (**9**, **11**, **13** and **14**) of 1-aminoindane-2-carboxylic acid, a new benzologue of cispentacin.

1. Introduction

Although of less importance than their α-analogues, β-amino acids are also present in peptides and different heterocycles, and their free forms and derivatives exhibit interesting pharmacological effects.[1–6] A decade ago, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin), an antifungal antibiotic, was isolated from *Bacillus cereus*[7] and *Streptomyces setonii*.[8] *cis*-2-Aminocyclopentanecarboxylic acid is also a component of the antibiotic amipurimycin.[9] The research groups of Seebach and Gellman recently reported oligopeptide chains which can fold into stable helical structures.[10,11] Gellman's group synthesised and investigated[12–14] *trans*-2-aminocyclopentane- and *trans*-2-aminocyclohexanecarboxylic acid oligomers which display a stable helical conformation.

Besides the fact that they themselves possess pharmacological activity, the alicyclic β-amino acids can be used as building blocks for the preparation of modified (unnatural) analogues of

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0957-4166/00/$ - see front matter
PII: S0957-4166(00)00375-X

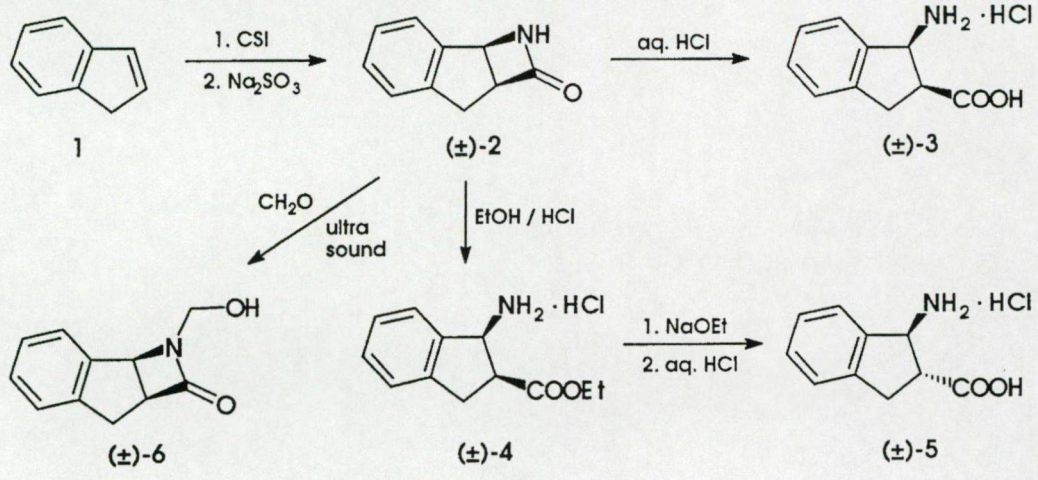
biologically active peptides. In consequence of the natural occurrence and the novel biological activity, chemical interest in investigations of the alicyclic β-amino acids has rapidly increased. Our present aim was the synthesis of the title alicyclic β-amino acids.

2. Results and discussion

2.1. Synthesis of the racemic β-amino acid substrates

The pathways of the syntheses of the racemic amino acids **3** and **5** are shown in Scheme 1. Chlorosulphonyl isocyanate addition[15–17] to indene takes places regio- and stereoselectively, in accordance with the Markovnikov orientation, resulting in β-lactam **2**. Treatment of **2** with hydrochloric acid resulted in amino acid hydrochloride **3**, while treatment with ethanolic hydrogen chloride led to ethyl ester **4**. Sodium ethoxide isomerisation of **4**, followed by acidic hydrolysis, resulted in the *trans* amino acid hydrochloride **5**. The free amino acids of **3** and **5** were liberated by ion-exchange chromatography.

The *N*-hydroxymethylated β-lactam **6**, the starting substance of the enzymatic reactions, was prepared from **2** with paraformaldehyde under sonication.



Scheme 1.

2.2. Enzymatic resolutions

N-Hydroxymethylated β-lactams were earlier readily resolved[18] by means of lipase AK- or lipase PS-catalysed asymmetric acylation of the primary hydroxy group at the (*S*) stereogenic centre. The investigated related substrates were: *N*-hydroxymethylated 7-azabicyclo[3.2.0]heptan-7-one, 7-azabicyclo[4.2.0]octan-8-one, 7-azabicyclo[4.2.0]oct-3-en-8-one and 7-azabicyclo[4.2.0]oct-4-en-8-one.[19,20] The enantioselectivities (*E*) varied in the range 40–200 when vinyl butyrate was used as acyl donor. Acetone proved to be the best solvent for the transformations.

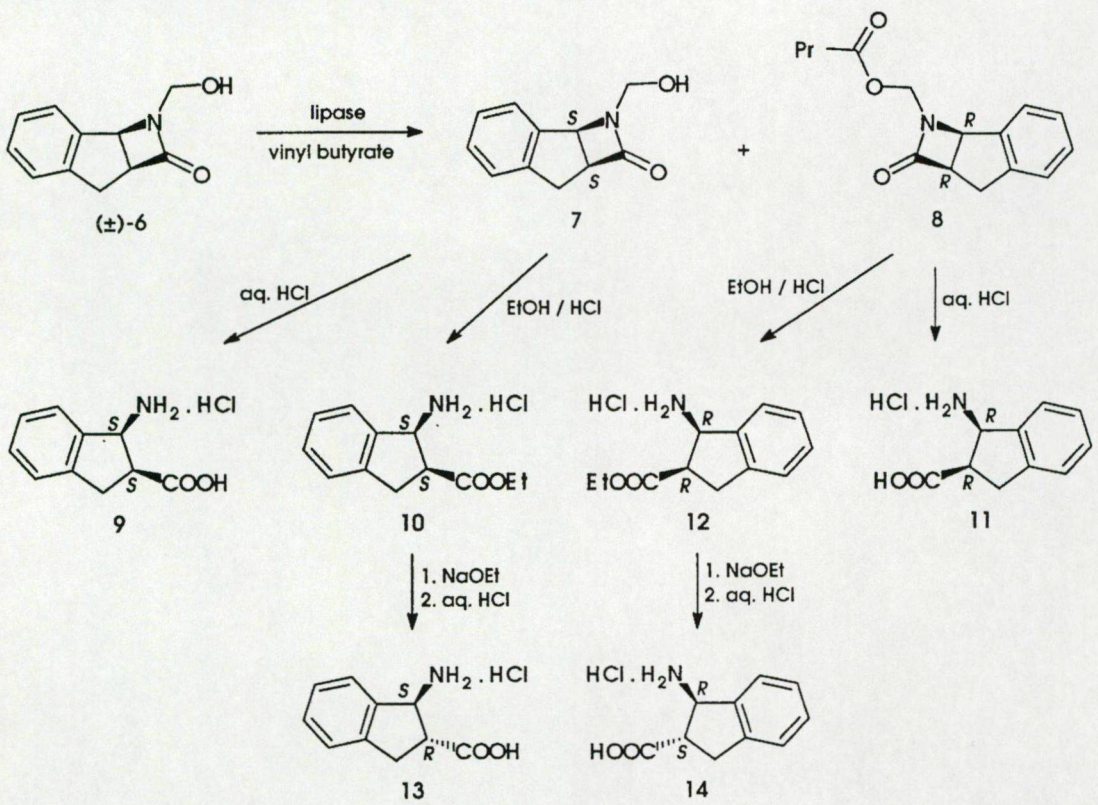
At the beginning of this work, we had some doubt as to whether similarly high selectivities would be achieved, since the steric demand of the benzologue of 7-azabicyclo[3.2.0]heptan-7-one is increased. In the small-scale experiments (Table 1), it was found that lipase AK and lipase PS are each excellent catalysts, both in vinyl acetate- and in vinyl butyrate-mediated acylation

(E>200). In the present case, replacement of acetone by acetonitrile or tetrahydrofuran did not lead to lower E values; excellent selectivities were still attained (E>200). Finally, for the gram-scale resolution of **6**, lipase AK and vinyl butyrate in THF were used. With this method, after a reaction time of 2.5 hours, product **8** was obtained in 44% yield, and substrate **7** in 42% yield, after chromatographic separation, both with ee = 99%.

Table 1
Effects of vinyl esters (0.2 M) and solvent on the acylation of **6** (0.1 M) in the presence of lipase PS[a] or AK[a] (50 mg ml^{-1}) at room temperature

Solvent	Acyl donor[b]	Enzyme	Time (h)	Conv. (%)	Ee_s (%)	Ee_p (%)	E
Acetone	VA	Lipase AK[a]	4	49	94	98	>200
Acetone	VB	Lipase AK[a]	7	47	88	99	>200
Acetone	VB	Lipase PS[a]	7	40	66	99	>200
THF	VB	Lipase PS[a]	7	46	85	98	>200
THF	VB	Lipase AK[a]	2.5	49	96	99	>200
Acetonitrile	VB	Lipase AK[a]	8	49	93	98	>200

[a] Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose.
[b] VA = vinyl acetate, VB = vinyl butyrate.



Scheme 2.

Enantiomers **7** and **8** were transformed to the corresponding β-amino acids **9** and **11** and esters **10** and **12**, similarly to the racemic compounds (Scheme 2). Isomerisation of esters **10** and **12**, followed by hydrolysis, resulted in the *trans* enantiomers **13** and **14**, respectively, with high optical purity (ee = 99%).

2.3. Absolute configurations

X-ray investigation revealed the absolute configuration of **12**. Amino ester **12** was transformed to thiourea **15** by reacting it with (1*S*,2*S*)-1,3-diacetoxy-1-(4-nitrophenyl)-2-propyl isothiocyanate (DANI), a newly developed chiral derivatising agent.[21,22] The X-ray structure (Fig. 1) clearly shows the (*R*,*R*) configuration of the starting **12**. In the early cases, *S* selectivity was observed[19,20] in the enzyme-catalysed acylation of hydroxymethylated β-lactams, while in the present case *R* selectivity was found. It is necessary to mention that in these reactions the same stereochemical demands are fulfilled around the asymmetric centres, but only the sequence of priority of the substituents on the substrates differs.

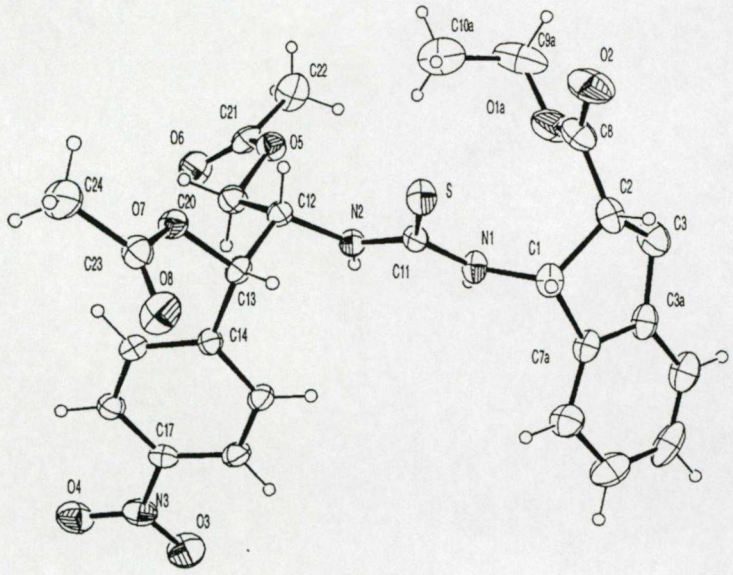


Figure 1. ORTEP plot of the X-ray structure of thiourea **15**. The thermal ellipsoids are drawn at the 25% probability level. Only the main component of the disordered ester chain is shown

3. Conclusions

Starting from indene, the syntheses of all four enantiomers of 1-aminoindane-2-carboxylic acid proved possible by a combination of lipase-catalysed *O*-acylation and some simple synthetic transformations. The synthesised β-amino acids, all four enantiomers (**9**, **11**, **13** and **14**) of 1-aminoindane-2-carboxylic acid, are promising compounds for the synthesis of partially saturated heterocycles, peptides and peptidomimetics, as potential pharmacons.

4. Experimental

4.1. Materials and methods

Vinyl acetate was purchased from Aldrich Chemical Co. and vinyl butyrate from Fluka. Lipase PS and lipase AK were obtained from Amano Pharmaceuticals, and Novozym 435 as an immobilised preparation from Novo Nordisk. Before use, lipase PS (5 g) was dissolved in Tris–HCl buffer (0.02 M; pH 7.8) in the presence of sucrose (3 g), followed by adsorption on Celite (17 g) (Sigma). The lipase preparation thus obtained contained 20% (w/w) of lipase.

The ee values of the unreacted alcohol **7** and the produced ester **8** and amino esters **10** and **12** were determined by gas chromatography on a Chrompack CP-Chirasil-DEX CB column (25 m). Amino esters **10** and **12** were derivatised with acetic anhydride in the presence of 4-dimethylaminopyridine and pyridine before the gas chromatographic analysis. The ee values of the amino acid enantiomers **9**, **11**, **13** and **14** were determined by HPLC on an APEX ODS column (0.46×25 cm, Jones Chromatography Ltd.), with 0.1% aqueous trifluoroacetic acid:methanol (45:55) as eluent. For chiral derivatisation, (1*S*,2*S*)-1,3-diacetoxy-1-(4-nitrophenyl)-2-propyl isothiocyanate was used, according to the literature.[21,22]

Optical rotations were measured with a Perkin–Elmer 341 polarimeter. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or to TSP (D_2O) as internal standards; multiplicities were recorded as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and om (overlapping multiplet). Melting points were determined on a Kofler apparatus.

4.2. 3,4-Benzo-6-azabicyclo[3.2.0]heptan-7-one, (±)-2

A solution of 15.57 g (0.11 mol) *N*-chlorosulphonyl isocyanate in dry diethyl ether (50 ml) was added rapidly to 11.62 g (0.10 mol) freshly distilled indene dissolved in dry diethyl ether (200 ml). The resulting colourless solution was stirred for 2 hours at room temperature, after which *n*-hexane (100 ml) was added and the crystalline product was filtered off. The crystalline *N*-chlorosulphonyl derivative was dissolved in diethyl ether (200 ml) and added, dropwise and with stirring, to a mixture of Na_2SO_3 (10 g) in water (50 ml) and diethyl ether (50 ml). During the addition, the aqueous phase was kept slightly alkaline by addition of 10% KOH solution. (±)-**2** crystallised out and was filtered off (7.92 g) from the mixture. A second crop of (±)-**2** was obtained as follows: from the above filtrate, the organic phase was separated, and the aqueous part was extracted twice with diethyl ether. The combined organic layer was dried (Na_2SO_4) and evaporated. The combined crude products were recrystallised from ethyl acetate–methanol, which afforded 10.03 g (63%) colourless crystals of (±)-**2**, mp 188–189°C, lit.[23] mp 183–184°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.07 (1H, dd, J=17.5, 10.5, CH_2), 3.35 (1H, d, J=17.4, CH_2), 4.02 (1H, m, C*H*CO), 5.03 (1H, d, J=4.2, C*H*N), 6.28 (1H, broad s, N*H*), 7.18–7.36 (4H, om, C_6H_4). Analysis: calculated for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80; found: C, 75.61; H, 5.91; N, 8.65.

4.3. cis-1-Aminoindane-2-carboxylic acid hydrochloride, (±)-3

The β-lactam (±)-**2** (1.59 g, 0.01 mol) was refluxed in 36% hydrochloric acid (10 ml) for 12 hours. After standing overnight, the precipitated crystalline product was separated by filtration and recrystallised from ethanol–diethyl ether (1.68 g, 79%), mp 220–222°C.

^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.37 (2H, d, J=8.9, CH_2), 3.74 (1H, dd, J=15.9, 8.7, CHCO), 5.01 (1H, d, J=7.0, CHN), 7.42 (3H, m, C_6H_4), 7.53 (1H, d, J=7.5, C_6H_4). Analysis: calculated for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; found: C, 56.35; H, 5.56; N, 6.72.

The free amino acid base was liberated by ion-exchange chromatography with DOWEX 50, mp 265–266°C.

^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.22 (1H, dd, J=16.3, 9.6, CH_2), 3.32 (1H, dd, J=16.3, 8.6, CH_2), 3.51 (1H, m, CHCO), 4.85 (1H, d, J=6.8, CHN), 7.37 (1H, m, C_6H_4), 7.44 (2H, m, C_6H_4), 7.51 (1H, d, J=7.5, C_6H_4). Analysis: calculated for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; found: C, 67.49; H, 6.48; N, 7.97.

4.4. *Ethyl* cis-*1-aminoindane-2-carboxylate hydrochloride, (±)-4*

The β-lactam (±)-**2** (0.01 mol, 1.59 g) was refluxed in ethanol (50 ml) containing 22% dry hydrogen chloride for 8 hours. The solvent was evaporated off, and the crystalline product was recrystallised from ethanol–diethyl ether (1.98 g, 82%), mp 210–211°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27 (3H, t, J=7.1, CH_3), 3.24 (1H, dd, J=18.0, 10.8, CHCH_2), 3.54 (2H, m, CHCH_2, CHCO), 4.20 (2H, q, J=7.1, OCH_2), 4.81 (1H, d, J=6.2, CHN), 7.25 (3H, m, C_6H_4), 7.80 (1H, d, J=7.6, C_6H_4). Analysis: calculated for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79; found: C, 59.82; H, 6.56; N, 5.43.

4.5. trans-*1-Aminoindane-2-carboxylic acid hydrochloride, (±)-5*

Sodium (0.60 g) was dissolved in dry ethanol (20 ml), 2.05 g (0.01 mol) base (±)-**4** was added to this solution and the mixture was heated at 70°C for 7 hours. The yellow solution was evaporated and refluxed with 10% hydrochloric acid (20 ml) for 10 hours. After standing overnight, the solution was filtered and evaporated to dryness. The residue was dissolved in hot methanol, and the removal of solvent gave 1.80 g crude product, which was recrystallised from ethanol–diethyl ether (1.45 g, 60%), mp 220–222°C.

^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.23 (1H, m, CH_2), 3.51 (2H, m, CH_2, CHCO), 5.17 (1H, d, J=5.3, CHN), 7.40 (3H, m, C_6H_4), 7.51 (1H, d, J=7.0, C_6H_4). Analysis: calculated for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; found: C, 56.44; H, 5.73; N, 6.40.

The free amino acid base was liberated by ion-exchange chromatography with DOWEX 50, mp 234–235°C.

^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.13 (1H, dd, J=16.0, 7.0, CH_2), 3.22 (1H, m, CH_2), 3.46 (1H, dd, J=16.0, 8.7, CHCO), 5.04 (1H, d, J=6.0, CHN), 7.40 (3H, m, C_6H_4), 7.48 (1H, d, J=7.4, C_6H_4). Analysis: calculated for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; found: C, 67.66; H, 6.38; N, 7.72.

4.6. *Preparation of racemic 3,4-benzo-6-hydroxymethyl-6-azabicyclo[3.2.0]heptan-7-one, (±)-6*

Compound **2** (6.00 g, 37.69 mmol) was dissolved in THF (250 ml), and paraformaldehyde (1.36 g), potassium carbonate (0.52 g, 3.77 mmol) and water (3.8 ml) were added. The solution was sonicated for 5 hours. The solvent was evaporated off and the residue was dissolved in ethyl acetate. The solution was dried over Na_2SO_4, the solvent was evaporated off and the product was recrystallised from a THF–diisopropyl ether mixture to afford white crystals of **6** (5.06 g, 71%,), mp 112–114°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.08 (2H, m, CHCH_2, OH), 3.33 (1H, d, J=17.4, CHCH_2), 4.01 (1H, m, CHCO), 4.39 (1H, dd, J=11.6, 9.0, CH_2OH), 4.87 (1H, dd, J=11.6, 5.8, CH_2OH), 5.17 (1H, d, J=4.3, CHN), 7.28 (3H, m, C_6H_4), 7.42 (1H, d, J=7.4, C_6H_4). Analysis: calculated for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40; found: C, 69.39; H, 6.23; N, 7.30.

4.7. General procedure for small-scale experiments

The *N*-hydroxymethyl-β-lactam (±)-**6** (0.1 M solution) in an organic solvent (1 ml) was added to lipase PS (50 mg ml^{-1}) or lipase AK (50 mg ml^{-1}). Vinyl acetate or butyrate (0.2 M in the reaction mixture) was added and the mixture was shaken at room temperature. The progress of the reaction was followed by taking samples from the reaction mixture at intervals and analysing them by gas chromatography.

4.8. Gram-scale resolution of (±)-6

Racemic **6** (4.00 g, 21.14 mmol) was dissolved in THF (200 ml), lipase AK (10.58 g) and vinyl butyrate (4.83 g, 42.28 mmol) were added and the mixture was stirred at room temperature. After 2.5 hours, a few drops of triethylamine were added in order to enhance the stability of the unreacted acid-labile **7**, and the enzyme was filtered off at 50% conversion. The THF was evaporated off. The residue was chromatographed on silica, with elution with dichloromethane:ethyl acetate (9:1) for separation of the ester (1*R*,5*R*)-**8** (2.43 g, 9.37 mmol; $[\alpha]_D^{25}$=−91.8 (c=0.51, $CHCl_3$); ee=99%) as a colourless oil. Elution with dichloromethane:ethyl acetate (1:1) afforded the unreacted (1*S*,5*S*)-**7** (1.68 g, 8.88 mmol; $[\alpha]_D^{25}$=+137 (c=0.36, $CHCl_3$); ee=99%; mp 138–140°C) as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **8**: 0.96 (3H, t, J=7.4, CH_3), 1.66 (2H, m, $CH_2CH_2CH_3$), 2.30 (2H, t, J=7.4, CH_2CH$_2$CH$_3$), 3.09 (1H, dd, J=17.4, 10.5, CHCH_2), 3.32 (1H, d, J=17.4, CHCH_2), 4.00 (1H, m, CHCO), 4.97 (1H, d, J=11.4, OCH_2), 5.07 (1H, d, J=11.4, OCH_2), 5.11 (1H, d, J=4.4, CHN), 7.30 (3H, m, C_6H_4), 7.61 (1H, d, J=7.4, C_6H_4). Analysis: calculated for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; found: C, 69.12; H, 6.71; N, 5.48.

The ^{1}H NMR data for **7** are similar to those for (±)-**6**. Analysis found: C, 69.71; H, 5.91; N, 7.35.

4.9. Acid hydrolysis of 7 and 8

Compound **7** (0.40 g, 2.11 mmol) was dissolved in 18% HCl (14 ml) and refluxed for 2 hours at 70°C. The solvent was evaporated off, and the residue was recrystallised from ethanol–diethyl ether, which afforded white crystals of (1*S*,2*S*)-**9** (0.35 g, 1.64 mmol; $[\alpha]_D^{25}$=+5.7 (c=0.50, MeOH); mp 281–282°C; ee=99%).

The ^{1}H NMR data for **9** are similar to those for (±)-**3**. Analysis found: C, 56.34; H, 5.58; N, 6.53.

Similarly, **8** (1.00 g, 3.86 mmol) afforded white crystals of (1*R*,2*R*)-**11** (0.50 g, 2.34 mmol; $[\alpha]_D^{25}$=−5.3 (c=0.50, MeOH); mp 273–275°C; ee=99%). The ^{1}H NMR data for **11** are similar to those for **9** and (±)-**3**. Analysis found: C, 56.29; H, 5.71; N, 6.60.

4.10. Preparation of esters 10 and 12

Similarly as in Section 4.4, (1*S*,5*S*)-**7** (0.80 g, 4.23 mmol) afforded white crystals of (1*S*,2*S*)-**10** (0.73 g, 3.02 mmol; $[\alpha]_D^{25}=+6.0$ ($c=0.50$, H_2O); mp 208–209°C; ee=99%). The ^1H NMR data for **10** are similar to those for (±)-**4**. Analysis found: C, 59.74; H, 6.61; N, 5.75.

Similarly, (1*R*,5*R*)-**8** (1.00 g, 3.86 mmol) afforded white crystals of (1*R*,2*R*)-**12** (0.70 g, 2.90 mmol; $[\alpha]_D^{25}=-6.2$ ($c=0.50$, H_2O); mp 214–216°C; ee=99%). The ^1H NMR data for **12** are similar to those for **10** and (±)-**4**. Analysis found: C, 59.69; H, 6.59; Cl, 14.62; N, 5.84.

4.11. Preparation of trans-1-aminoindane-2-carboxylic acid hydrochloride enantiomers 13 and 14

With the procedure described in Section 4.5, (1*S*,2*S*)-**10** (0.40 g, 1.65 mmol) afforded (1*S*,2*R*)-**13** crude material. Since the product contained ~20% *cis* isomer, the isomerisation was carried out again, yielding white crystals of (1*S*,2*R*)-**13** (0.13 g, 0.61 mmol; $[\alpha]_D^{25}=-76.8$ ($c=0.5$, H_2O); mp 217–220°C; ee=99%). The ^1H NMR data for **13** are similar to those for (±)-**5**. Analysis found: C, 56.11; H, 5.69; Cl, 16.47; N, 6.48.

With the above procedure, (1*R*,2*R*)-**12** (0.40 g, 1.65 mmol) afforded (1*R*,2*S*)-**14** (0.21 g, 0.98 mmol; $[\alpha]_D^{25}=+75.8$ ($c=0.5$, H_2O); mp 220–222°C; ee=99%). The ^1H NMR data for **14** are similar to those for **13** and (±)-**5**. Analysis found: C, 56.28; H, 5.62; Cl, 16.52; N, 6.61.

4.12. Preparation of thiourea derivative 15

The free base of ethyl ester **12** (0.08 g, 0.39 mmol) was dissolved in diethyl ether (10 ml), and (1*S*,2*S*)-1,3-diacetoxy-1-(4-nitrophenyl)-2-propyl isothiocyanate (0.14 g, 0.41 mmol) was added. The mixture was allowed to stand at room temperature for a few hours. The white crystals of **15** were separated. The product was recrystallised from diisopropyl ether–diethyl ether, mp 145–148°C.

4.13. X-ray crystallography

All data were collected on a Rigaku AFC5S diffractometer, with graphite-monochromated Mo Kα radiation ($\chi=0.71069$ Å) in the ω–2θ scan mode at room temperature. The lattice parameters were calculated by least-squares refinements of 20 reflections. The weak reflections [$I<10\sigma(I)$] were rescanned up to two times. For **15**, 2819 reflections were collected ($2\theta_{max}=50°$). The data were corrected for Lorentz and polarisation effects.

4.13.1. Crystal data for 15

$C_{26}H_{27}N_3O_8S$, $M_r=541.57$, orthorhombic, space group $P2_12_12_1$ (no. 19), lattice parameters: $a=11.127(4)$, $b=22.908(3)$, $c=10.665(4)$ Å, $Z=4$, $V=2718.6(14)$ Å^3, $D_c=1.323$ g cm^{-3}, μ (Mo Kα)=0.172 mm^{-1}, $F(000)=1136$, $T=294$ K; a colourless plate, crystal dimensions 0.22×0.24×0.32 mm.

The structure was solved by direct methods (SIR-92)[24] and refined by full-matrix least-squares techniques (SHELXL-97)[25] to an R_1 value of 0.048 ($wR_2=0.112$). These final R values are based on the reflections with $I>2\sigma(I)$. The heavy atoms were refined anisotropically. The hydrogen atoms on the aliphatic carbons (C1, C2, C12 and C13) and on the nitrogen atoms were refined

with fixed isotropic temperature factors ($1.2U_{eq}$ of the carrying atom) and the remaining hydrogen atoms were included in the calculated positions with fixed isotropic temperature factors (1.2 or 1.5 times U_{eq} of the carrying atom). The ester group at C8 has two orientations. The population of the major component is 56(5)%. Calculations were performed with teXsan for Windows[26] crystallographic software. Fig. 1 was drawn with ORTEP-3 for Windows.[27]

Acknowledgements

The authors would like to thank the OTKA (grant no. T 030452) and MKM (grant no. FKFP 0535/1999) for financial support.

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IV.

Monatshefte für Chemie 133, 1423–1430 (2002)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Imidazo[1′,5′:1,2]pyrido [3,4-*b*]indole Derivatives

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Summary. The reactions of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid and its ethyl ester with alkyl and aryl isothiocyanates under mild conditions resulted in the corresponding thiohydantoin-fused tetrahydro-β-carbolines. Treatment of the ethyl ester with isocyanates furnished ethyl 2-alkyl- or arylcarbamoyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylates which were transformed to hydantoin-fused tetrahydro-β-carbolines. The structures of the thiohydantoin compounds, involving two conformers and the presence of keto-enol tautomerism, were determined by NMR spectroscopy.

Keywords. β-Carbolines; Hydantoins; Thiohydantoins; Keto-enol tautomerism.

Introduction

The β-carboline structure is present in important natural compounds, and its derivatives exert various pharmacological effects on the benzodiazepine receptors in the mammalian nervous system [1–4]. It is also found as a structural element of compounds exerting anticancer potential, analgesic activity, or oxytocin antagonism [5]. In 1994, in a programme with the goal of developing new drugs affecting the central nervous system, *Lopez-Rodriguez et al.* have studied the ring-closure possibilities of the 1,2,3,4-tetrahydro-β-carboline skeleton through the reaction of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (**1**) with alkyl and aryl isocyanates under vigorous conditions (refluxing for 40 h in acetone or *DMSO*). In their case the corresponding hydantoin analogues have been formed [6]. Some further derivatives of the 4-ring hydantoins exert pharmacological effects on α_1-adrenoreceptors [7]. However, the synthesis of thiohydantoin derivatives remained unsolved under the circumstances applied: in the reactions of **1** and isothiocyanates, decarboxylation took place, and open-chain thiourea derivatives have been isolated instead of the desired thiohydantoins [6].

Our present aim is to attempt the synthesis of thiohydantoin-fused imidazo [1′,5′:1,2]pyrido[3,4-*b*]indole derivatives under mild conditions based on the results of similar ring closures [8–13], starting from ethyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**2**).

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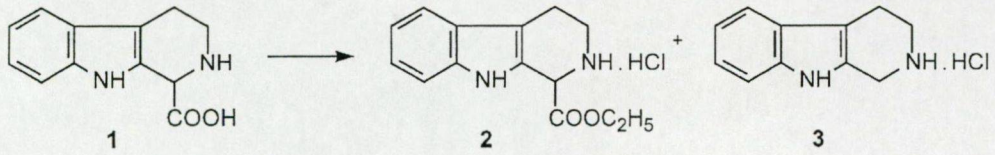
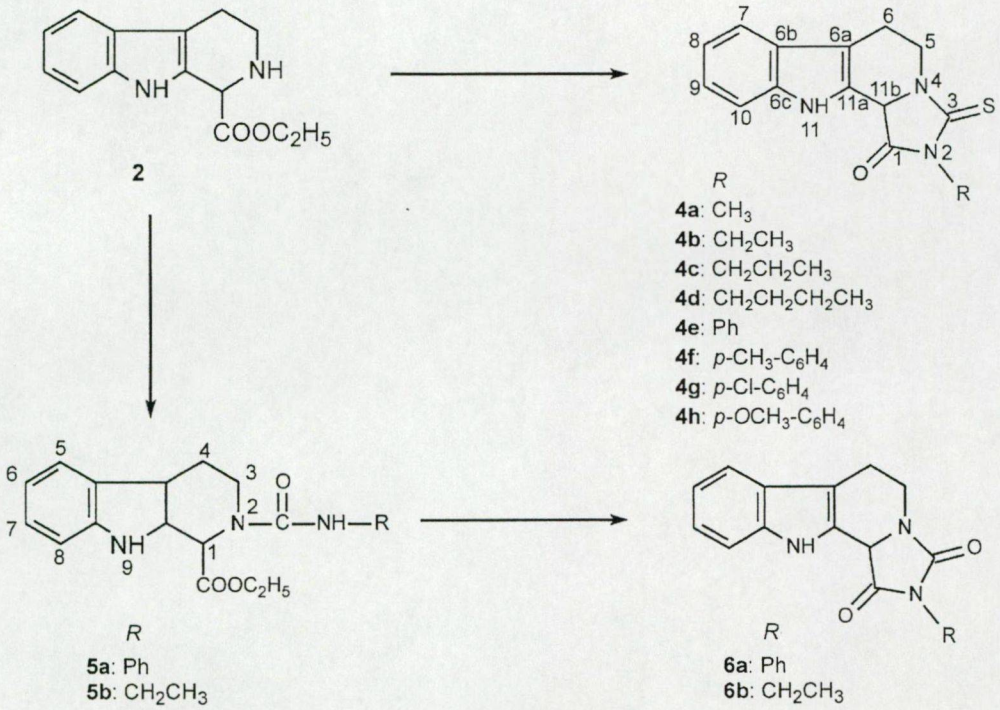
Results and Discussion

1,2,3,4-Tetrahydro-β-carboline-1-carboxylic acid (**1**) was obtained from tryptamine hydrochloride and glyoxylic acid [14]. Racemic **1** was esterified by two methods (Scheme 1): refluxing in ethanol with thionyl chloride (method A) or reaction with dry hydrogen chloride gas in ethanol (method B) [14]. Both methods resulted besides **2** in a by-product, the hydrochloride of 1,2,3,4-tetrahydronorharmane (**3**) as a consequence of decarboxylation. This side-product could be filtered off from the hot ethanolic solutions. Method A gave **2** in a somewhat higher yield (A: 76%, B: 57%).

When the ester base **2** was combined with alkyl and aryl isothiocyanates at room temperature in methanol, the corresponding target thiohydantoins **4** could be filtered off from the reaction mixtures after stirring overnight (Scheme 2). Generally, the yields were fair to good (41–74%), except in the case of **4d** where it was only 16%. No decarboxylation was observed during the reactions, and no



Scheme 1



Scheme 2

intermediates or by-products could be isolated from the residues. From the reactions of **1** and isothiocyanates under the same conditions, but with sodium methylate as the catalyst, the thiohydantoins **4** were obtained in rather low yields.

In the reactions of **2** and ethyl and phenyl isocyanates under similarly mild conditions, the corresponding urea derivatives **5** were formed as crystalline products. These were cyclized by refluxing in ethanol for one day under hydrochloric acid catalysis. Hydantoin compounds **6a** and **6b** were formed in 56 and 37% yield; and no other products could be isolated.

The low solubility and susceptibility to degradation of **4a–h** made the proof of the thiohydantoin structure by NMR spectroscopy difficult. Hydantoin derivatives can undergo keto-enol tautomerism [6]. In addition, the saturated nitrogen containing heterocycles tend to populate more than one low-energy conformation in solution due to the relative ease of nitrogen inversion [15]. Bearing in mind the above possible processes, the observed line broadening in pyridine-d_5 at 300 K was not surprising. In order to slow down the chemical exchange we decreased the temperature to 243 K. At this temperature two exchanging species were observed. The results of ^{1}H and ^{13}C resonance assignment by means of COSY, HSQC, and HMBC for **4b** as an example demonstrated that the two species have the same spin connectivity and similar chemical shifts. Concerning the constitution, the missing H-11b signal and the chemical shift values for C-11b (71.25 and 67.96 ppm) pointed to the predominance of the enol form for both species; however, the presence of the keto form cannot be excluded. In addition to the arguments described above, the ^{13}C chemical shifts relating to C-1 (170.06 and 169.03 ppm) are between the values for the possible enol (*ca.* 90 ppm) and keto (*ca.* 220 ppm) forms. The chemical shifts of C-11b (71.25 and 67.96 ppm) are also

Table 1. ^{1}H and ^{13}C NMR data of the conformers **4bA** and **4bB** dissolved in pyridine-d_5

	4bA δ/ppm		**4bB** δ/ppm	
	^{1}H	^{13}C	^{1}H	^{13}C
1	–	170.06	–	169.03
3	–	182.8	–	184.74
5	2.52, 4.98	40.46	3.88, 5.44	42.62
6	2.44, 2.84	20.21	2.76, 2.93	19.94
6a	–	112.45	–	111.65
6b	–	125.85	–	126.21
6c	–	138.24	–	138.30
7	6.96	112.23	7.35	120.17
8	7.05	123.36	7.74	119.64
9	7.17	119.18	7.43	112.8
10	7.51	118.92	7.33	123.48
11	12.4	–	13.41	–
11a	–	121.94	–	122.75
11b	–[b]	71.25[a]	–[b]	67.96[a]

[a] δ values between those for the enol (80 ppm) and keto (56 ppm) forms (C-11b) [5]; [b] the methine proton at C-11b is missing because of the suggested keto-enol tautomerism and HD exchange

average values in both species between the chemical shifts found in the literature [6] for the enol (80 ppm) and keto (56 ppm) forms. These observations, together with the missing H-11b, suggest a rapid acid-catalyzed equilibrium between the two tautomeric forms in both conformers. From these data we may conclude that the NMR signals belong to two exchanging conformational isomers which are predominantly the enol forms of the thiohydantoin derivatives. The two conformers are designated by **4bA** and **4bB**; the chemical shifts given in Table 1.

In $CDCl_3$ solutions of **4**, broadened signals were obtained which would also suggest the possibility of a conformational equilibrium. The compounds **4** were satisfactorily soluble in *DMSO*-d_6, where characteristic but still slightly broadened signals appeared. The geometry of the two conformations could not be established, but the conformational equilibrium is obviously due to nitrogen inversion [15].

Conclusions

It was proven that 2-substituted 5,6,11,11b-tetrahydro-1-oxo-1*H*-imidazo[1′,5′:1,2] pyrido[3,4-*b*]indole-3-thiones **4** can be prepared under mild conditions from 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (**1**) and its ethyl ester **2**. The structures of the thiohydantoin compounds, involving two conformers and the presence of keto-enol tautomerism, were determined by NMR spectroscopy.

Experimental

Melting points were determined with a Kofler apparatus at a heating rate of 4°C/min; the values are not corrected. ^{1}H NMR spectra were recorded in 5 mm tubes in the appropriate solvents on a Bruker DRX 400 instrument at 400 MHz. IR spectra were measured in KBr disks on a Perkin Elmer Paragon 1000PC FT-IR spectrometer. Analytical data were obtained by a Heraeus apparatus; they were in favourable agreement with the calculated values. The cyanates and isothiocyanates used were commercial products (Aldrich, Fluka). Yields in parentheses refer to reactions starting from **1**.

Ethyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**2**)

Method A: Absolute EtOH (18 cm^3) was cooled below − 10°C. $SOCl_2$ (1.59 cm^3, 21.8 mmol) was added dropwise, the temperature being kept below − 10°C. Then, **1** (4.3 g, 19.8 mmol) was added to the mixture, which was first stirred for 0.5 h at 0°C and then for 3 h at room temperature, and finally refluxed for 1 h.

Method B [14]: A suspension of 7.33 g dried and well-powdered **1** (33.8 mmol) in 150 cm^3 absolute EtOH was saturated with dry HCl gas under stirring, and the mixture was then refluxed for 2 h.

The crystalline product was filtered off from the hot solution in both cases and was identified as 1,2,3,4-tetrahydronorharmane (**3**; A: 1.28 g, 6.1 mmol, 18%; B: 2.45 g, 11.7 mmol, 35%). EtOH was evaporated under reduced pressure, and diethyl ether was added to promote crystallization. From the hydrochloride, the free base was obtained by treatment with aqueous NaOH and extraction with $CHCl_3$ followed by drying (Na_2SO_4) and evaporation. The product was purified by column chromatography on silica gel with a mixture of toluene: MeOH = 4:1 as the eluent. Method A resulted in a yield of 76% **2**, whereas method B gave a yield of 57%.

Yellowish needles; m.p.: 107–110°C (Et_2O; Ref. [14]: m.p.: 110–111°C); IR (KBr): $\bar{\nu} = 3363$, 1715, 1252 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.25$ (t, $J = 7.05$ Hz, CH_3), 2.54–2.63 (m, H-6a,b),

2.95–3.05 (m, H-5a), 3.06–3.16 (m, H-5b), 4.08–4.23 (m, CH_2), 4.67 (s, H-11b), 6.95 (t, $J = 7.30$ Hz, H-8), 7.04 (t, $J = 7.30$ Hz, H-9), 7.33 (d, $J = 7.8$ Hz, H-7), 7.39 (d, $J = 7.8$ Hz, H-10), 10.64 (s, H-11) ppm.

2-Substituted 5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1',5':1,2]pyrido[3,4-b]indole-3-thiones (**4a–4h**)*; general procedure*

The appropriate isothiocyanate (0.8 mmol) was added to 195 mg (0.8 mmol) **2** dissolved in 40 cm^3 MeOH. The mixture was stirred overnight, and the crystalline product was filtered off and recrystallized. The synthesis was repeated from the acid **1** in every case, the same method being used with the application of 1.6 mmol sodium methylate as catalyst. The analytical data were identical.

2-Methyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1',5':1,2]pyrido[3,4-b]indole-3-thione (**4a**; $C_{14}H_{13}N_3OS$)

Light-pink crystals; m.p.: 195–200°C ($EtOH/CHCl_3$); yield: 66% (16%); IR (KBr): $\bar{\nu} = 3447$, 3399, 3373, 1742, 1728, 1311 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.68$–2.88 (m, H-6a,b), 2.95 (bs, H-5a), 3.21 (s, CH_3), 4.92 (m, H-5b), 7.02 (t, $J = 7.55$ Hz, H-8), 7.15 (t, $J = 7.55$ Hz, H-9), 7.46 (d, $J = 7.55$ Hz, H-7), 7.5 (d, $J = 7.55$ Hz, H-10), 10.52 (s, H-11) ppm.

2-Ethyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1',5':1,2]pyrido[3,4-b]indole-3-thione (**4b**; $C_{15}H_{15}N_3OS$)

White crystals; m.p.: 203–211°C ($EtOH/CHCl_3$); yield: 62% (27%); IR (KBr): $\bar{\nu} = 3460$, 3389, 1742, 1727, 1271 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.19$ (t, $J = 7.30$ Hz, CH_3), 2.68–2.85 (m, H-6a,b), 2.91 (bs, H-5a), 3.72–3.91 (m, CH_2), 4.91 (m, H-5b), 7.03 (t, $J = 7.3$ Hz, H-8), 7.16 (t, $J = 7.30$ Hz, H-9), 7.47 (d, $J = 7.8$ Hz, H-7), 7.52 (d, $J = 7.8$ Hz, H-10), 10.49 (s, H-11).

2-Propyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1',5':1,2]pyrido[3,4-b]indole-3-thione (**4c**; $C_{16}H_{17}N_3OS$)

White crystals; m.p.: 188–190°C ($EtOH/CHCl_3$); yield: 41% (19%); IR (KBr): $\bar{\nu} = 3451$, 3389, 1743, 1727 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 0.87$ (t, $J = 7.55$ Hz, CH_3), 1.66 (m, CH_2), 2.63–2.88 (m, H-6a,b), 2.96 (bs, H-5a), 3.61–3.83 (m, CH_2), 4.92 (m, H-5b), 7.48 (d, $J = 8.3$ Hz, H-7), 7.02 (t, $J = 7.3$ Hz, H-8), 7.15 (t, $J = 7.8$, H-9), 7.51 (d, $J = 7.8$, H-10), 8.31 (bs, H-11) ppm.

2-Butyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1',5':1,2]pyrido[3,4-b]indole-3-thione (**4d**; $C_{17}H_{19}N_3OS$)

White crystals; m.p.: 186–188°C ($EtOH/CHCl_3$); yield: 16% (5%); IR (KBr): $\bar{\nu} = 3456$, 3387, 1743, 1724 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 0.90$ (t, $J = 7.30$ Hz, CH_3), 1.23–1.35 (m, CH_2), 1.55–1.69 (m, CH_2), 2.63–2.87 (m, H-6a,b), 2.96 (bs, H-5a), 3.66–3.87 (m, CH_2), 4.91 (m, H-5b), 7.03 (t, $J = 7.55$ Hz, H-8), 7.15 (t, $J = 7.55$, H-9), 7.46 (d, $J = 8.06$ Hz, H-7), 7.52 (d, $J = 8.06$ Hz, H-10), 10.44 (s, H-11) ppm.

2-Phenyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo [1',5':1,2]pyrido[3,4-b]indole-3-thione (**4e**; $C_{19}H_{15}N_3OS$)

Light-pink crystals; m.p.: 208–214°C ($EtOH/CHCl_3$); yield: 57% (31%); IR (KBr): $\bar{\nu} = 3423$, 3371, 3250, 1754, 1744, 1285 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.77$–2.90 (m, H-6a), 2.90–3.02 (m, H-6b),

3.12 (bs, H-5a), 5.12 (bs, H-5b), 7.06 (t, $J = 7.81$, H-8), 7.17 (t, $J = 7.81$, H-9), 7.30–7.37 (m, H-7 and H-10), 7.46–7.58 (m, phenyl), 10.54 (s, H-11) ppm.

2-(p-Tolyl)-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1',5':1,2]pyrido[3,4-b]indole-3-thione (**4f**; $C_{20}H_{17}N_3OS$)

Light-brown crystals; m.p.: 187–189°C (EtOH/$CHCl_3$); yield: 67% (36%); IR (KBr): $\bar{\nu} = 3442$, 3408, 1752, 1736, 1284 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.35$ (s, CH_3), 2.78–2.88 (m, H-6a), 2.89–3.00 (m, H-6b), 3.10 (s, H-5a), 5.11 (bs, H-5b), 7.05 (t, $J = 7.55$, H-8), 7.12–7.23 (m, H-9, H-7 and H-10), 7.31 (d, $J = 8.06$ Hz, phenyl), 7.52 (d, $J = 7.81$ Hz, phenyl), 10.51 (s, H-11) ppm.

2-(p-Chlorophenyl)-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1',5':1,2]pyrido [3,4-b]indole-3-thione (**4g**; $C_{19}H_{14}ClN_3OS$)

Light-pink crystals; m.p.: 202–209°C (EtOH/$CHCl_3$); yield: 59% (28%); IR (KBr): $\bar{\nu} = 3419$, 3396, 1745, 1730, 1281, 1253 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.76$–3.01 (m, H-6a,b), 3.08 (bs, H-5a) 5.09 (bs, H-5b), 7.06 (t, $J = 7.55$ Hz, H-8), 7.17 (t, $J = 7.55$ Hz, H-9), 7.39 (d, $J = 8.56$ Hz, phenyl), 7.49–7.56 (m, H-7 and H-10), 7.62 (d, $J = 8.56$ Hz, phenyl), 10.56 (s, H-11) ppm.

2-(p-Methoxyphenyl)-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1',5':1,2]pyrido [3,4-b]indole-3-thione (**4h**; $C_{20}H_{17}N_3O_2S$)

Light-brown crystals; m.p.: 183–185°C (EtOH/$CHCl_3$); yield: 74% (21%); IR (KBr): $\bar{\nu} = 3363$, 1715, 1252, 1246, 1236 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.73$–3.01 (m, H-6a,b), 3.10 (bs, H-5a), 3.32 (s, OCH_3), 5.10 (bs, H-5b), 6.95–7.09 (m, H-8, H-7 and H-10), 7.16 (t, $J = 7.55$ Hz, H-9), 7.24 (d, $J = 7.81$ Hz, phenyl), 7.53 (d, $J = 7.81$ Hz, phenyl), 10.51 (s, H-11) ppm.

2-Substituted ethyl carbamoyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylates (**5a,b**)*; general procedure*

The appropriate isocyanate (0.8 mmol) was added to 195 mg (0.8 mmol) **2** dissolved in 40 cm^3 MeOH. The mixture was stirred overnight, and the crystalline product was filtered off and recrystallized from EtOH and diethyl ether.

Ethyl 2-ethylcarbamoyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**5a**; $C_{17}H_{21}N_3O_3$)

Pale-yellow crystals; m.p.: 167–170°C (EtOH/Et_2O); yield: 66%; IR (KBr): $\bar{\nu} = 3338$, 3290, 1726, 1606 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.19$ (t, $J = 7.3$ Hz, CH_3), 1.30 (t, $J = 7.3$ Hz, CH_3, ester), 2.76–2.94 (m, H-6a,b), 3.30–3.39 (m, CH_2), 3.53 (ddd, $J = 4.53$, 11.33, 13.6 Hz, H-5a), 3.92 (ddd, $J = 1.51$, 5.04, 13.6 Hz, H-5b), 4.18–4.31 (m, CH_2, ester), 4.65 (t, $J = 4.5$ Hz, H-11b), 5.93 (s, NH), 7.11 (t, $J = 7.8$ Hz, H-8), 7.2 (t, $J = 7.81$ Hz, H-9), 7.36 (d, $J = 7.8$ Hz, H-7), 7.49 (d, $J = 7.8$ Hz, H-10), 8.28 (s, H-11) ppm.

Ethyl 2-phenylcarbamoyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**5b**; $C_{21}H_{21}N_3O_3$)

Pale-yellow crystals; m.p.: 145–150°C (EtOH/Et_2O); yield: 61%; IR (KBr): $\bar{\nu} = 3386$, 3289, 1723, 1630, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.31$ (t, $J = 7.3$ Hz, CH_3), 2.84–3.03 (m, H-6a,b), 3.67 (ddd, $J = 4.28$, 11.83, 13.6 Hz, H-5a), 4.13 (ddd, $J = 1.02$, 5.04, 13.6 Hz, H-5b), 4.23–4.32 (m, CH_2), 5.99 (bs, H-11b), 6.62 (s, NH), 7.06 (t, $J = 7.55$ Hz, phenyl), 7.13 (t, $J = 7.3$ Hz, H-8), 7.21 (t, $J = 8.06$ Hz, H-9), 7.31 (t, $J = 7.3$ Hz, phenyl), 7.36–7.41 (m, phenyl and H-7), 7.51 (d, $J = 8.06$ Hz, H-10), 8.31 (s, H-11) ppm.

2-Substituted 5,6,11,11b-tetrahydro-1H-imidazo[1',5':1,2]pyrido[3,4-b]indole-1,3(2H)-diones (**6a,b**)*; general procedure*

The appropriate carbamoyl compounds **5a** or **5b** (50 mg) were refluxed in 25 cm^3 EtOH containing 4% dry HCl for one day. The reaction mixture was evaporated, diethyl ether was added, and the crystalline product was filtered off and recrystallized.

2-Ethyl-5,6,11,11b-tetrahydro-1H-imidazo[1',5':1,2]pyrido[3,4-b] indole-1,3(2H)-dione (**6a**)

Pale-yellow crystals; m.p.: 182–184°C ($EtOH/H_2O$; Ref. [6]: m.p.: 184°C); yield: 56%.

2-Phenyl-5,6,11,11b-tetrahydro-1H-imidazo[1',5':1,2]pyrido[3,4-b]indole-1,3(2H)-dione (**6b**; $C_{19}H_{15}N_3O_2$)

Pale-yellow crystals; m.p.: 239–241°C ($EtOH/H_2O$; Ref. [6]: m.p.: 241°C); yield: 37%; IR (KBr): $\bar{\nu} = 3412$, 1772, 1704 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.89$ (ddd, $J = 1.26$, 4.53, 15.86 Hz, H-6a), 2.99–3.12 (m, H-6b), 3.33 (ddd, $J = 5.04$, 11.58, 13.6 Hz, H-5a), 4.64 (dd, $J = 6.04$, 13.6 Hz, H-5b), 5.39 (t, $J = 1.76$ Hz, H-11b), 7.16 (t, $J = 7.55$ Hz, H-8), 7.25 (t, $J = 7.81$ Hz, H-9), 7.33–7.48 (m, phenyl and H-7), 7.53 (d, $J = 7.8$ Hz, H-10), 8.51 (s, H-11) ppm.

Acknowledgement

The authors' thanks are due to OTKA (grants No. T030452 and T034901) for financial support.

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Received February 2, 2002. Accepted (revised) March 4, 2002

V.

Synthesis and Stereochemistry of Indano[1,2-*d*][1,3]oxazines and Thiazines, New Ring Systems

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Received September 10, 2003

A set of structurally varied indano[1,2-*d*][1,3]oxazines and thiazines, which are new ring systems, were prepared by ring-closure reactions of amino alcohols **4-6**. The reactions of *cis*- and *trans*-1-amino- and *cis*-1-benzylamino-2-hydroxymethylindane (**4-6**) with 1 equivalent of an aromatic aldehyde in methanol at room temperature resulted in three-component equilibria (**15a-g**), or a Schiff base (**16**), or a ring-closure product alone (**17a-c**), respectively, depending on the substitution or configuration of the starting amino alcohol. The ring-chain tautomeric equilibria can be described by an equation of Hammett type.

J. Heterocyclic Chem., **41**, 69 (2004).

Introduction.

Cyclic β-amino acids can be used as starting substances for the preparation of different heterocycles, potential pharmacons and synthons of natural products or their analogues, also used as building blocks in drug research [1-4]. (1*R*,2*S*)-2-Aminocyclopentanecarboxylic acid (cispentacin) is an antifungal antibiotic [5-9], while many 1,2- and 1,3-amino alcohols and their derivatives play important roles in the synthesis of pharmacologically active compounds [10-14]. The applications of *cis*-1-amino-2-indanol in asymmetric syntheses have been reviewed [15], and its (1*S*,2*R*) enantiomer is a key component of an HIV protease inhibitor, Indinavir [16,17].

Our present aim was to prepare *cis*- and *trans*-1-amino-2-hydroxymethylindane from 1-aminoindane-2-carboxylic acid derivatives (new cispentacin benzologues) and to examine the chemistry and stereochemistry of indane-fused 1,3-oxazines and thiazines.

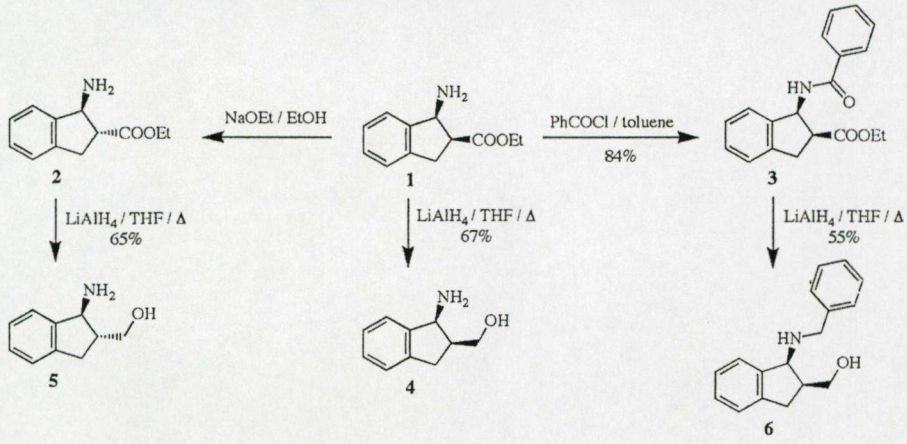
Results and Discussion.

In our earlier work, racemic ethyl *cis*- and *trans*-1-aminoindane-2-carboxylate (**1** and **2**) were prepared from indene by chlorosulfonyl isocyanate addition, followed by ring opening and isomerization [18]. The *cis*- and *trans*-unsubstituted and *cis*-*N*-benzyl-substituted 1,3-amino alcohols **4-6** were prepared by $LiAlH_4$ reduction or by benzoylation followed by reduction, respectively (Scheme 1).

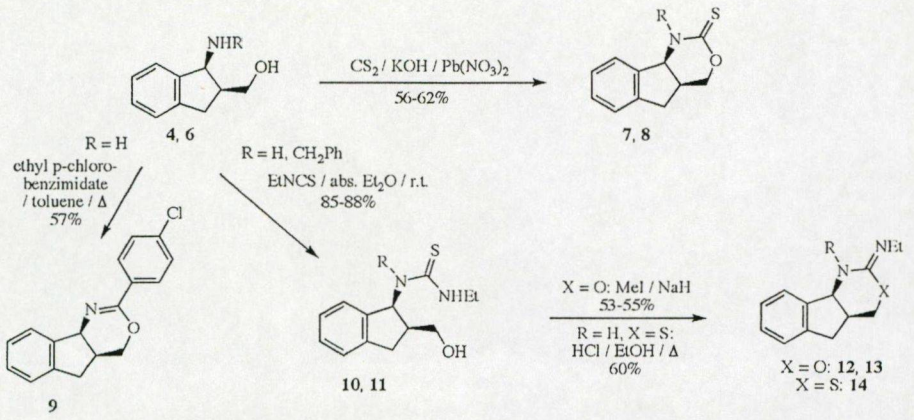
For the preparation of 2-thioxo-1,3-oxazines **7** and **8** the most common method is the reaction of the appropriate 1,3-amino alcohols **4** and **6** with carbon disulfide, followed by cyclization of the resulting thiourea with lead(II) nitrate. Cyclization of the corresponding 1,3-amino alcohol **4** with ethyl *p*-chlorobenzimidate resulted in the dihydro-1,3-oxazine **9**. The synthesis of heterocycles **12-14** started from adducts of the corresponding amino alcohols **4** and **6** with ethyl isothiocyanate. Treatment of thioureas **10** and **11** with methyl iodide followed by alkali treatment led to the elimination of methyl mercaptan, resulting in the oxazines **12** and **13** in good yields. Treatment of thiourea **10** with ethanolic hydrogen chloride under reflux, followed by treatment with alkali provided thiazine **14** (Scheme 2).

The *cis* amino alcohol **4** was condensed in methanolic solution with seven substituted aromatic aldehydes with

Scheme 1



Scheme 2

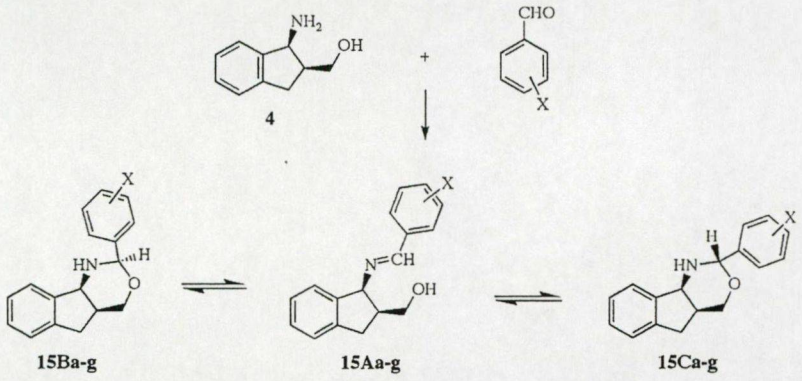


different electronic characters. The reactions reached completion within a few hours, even at room temperature. After evaporation and purification, well-defined products **15a-g** were obtained, which existed as three-component tautomeric mixtures in deuteriochloroform solution. For the tautomeric equilibria to be reached, the substances were allowed to stand for 24 h in deuteriochloroform (Scheme 3). The relative configurations of the various structures **15A,B,C** were determined *via* NOESY spectra, on the basis of observation of NOE correlation's between the NH-C*H*Ar-O and the NH-C*H*-CH hydrogen atoms.

oxazines. When eq. (1) was applied to the log K_X values, good linear correlations were obtained *vs* the Hammett-Brown parameter (σ^+) of the substituent X on the 2-phenyl group for compounds **15a-g** (Tables 1 and 2, Figure 1). The tautomeric ratios are based on the integration of the **15B** and **15C** ring form NH-C*H*Ar-O and the **15A** chain form N=CH proton singlets.

The linear regression analysis data in Table 2 show that, as customary among 2-aryl-substituted tetrahydro-1,3-oxazines, the value of ρ is positive in each case; *i.e.* an electron-withdrawing substituent on the 2-aryl ring

Scheme 3



X = *p*-NO_2: **a**; *m*-Br: **b**; *p*-Cl: **c**; H: **d**; *p*-Me:**e**; *p*-OMe: **f**; *p*-NMe_2: **g**

Comparative studies were carried out earlier on the ring-chain tautomerism of a wide range of 2-aryl-substituted tetrahydro-1,3-oxazines [19-24]. For all these series, the following equation is valid:

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad (1)$$

where K_X = [ring]/[chain] and ρ is a constant characteristic of the ring system. In deuteriochloroform solution at ambient temperature, ρ is 0.76 for tetrahydro-1,3-

favours the ring-closed tautomer. The proportion of the ring form for the *trans*-2-aryl-1,3-*O,N* heterocycles **15C** varies within a somewhat wider range (10.7-54%) than that for the corresponding *cis*-2-aryl-1,3-*O,N* heterocycles **15B** (9.2-41.7%). The relative configuration of the ring-closed products does not seem to influence the value of ρ: *cis*- and *trans*-2-aryl-1,3-*O,N* heterocycles have very similar values of ρ (0.78 and 0.81).

Table 1

Proportions (%) of Ring Forms (**B** and **C**) in Tautomeric Equilibria for Compounds **15a-g** in Deuteriochloroform at 300 K

Compound	X	σ^+	B (%)	C (%)
15a	pNO$_2$	0.79	41.7	54.0
15b	mBr	0.05	39.3	49.8
15c	pCl	0.114	35.8	50.5
15d	H	0	35.1	41.5
15e	pMe	-0.31	29.6	35.9
15f	pOMe	-0.77	22.9	28.2
15g	pNMe$_2$	-1.7	9.2	10.7

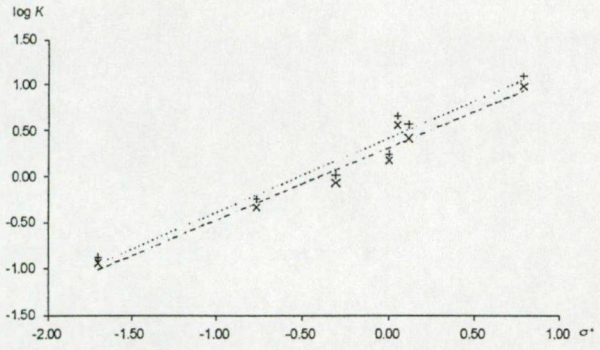


Figure 1. Plots of log K_X *vs* σ^+ for Compounds **15a-g**: **B** (X), **C** (+) in deuteriochloroform.

Table 2

Linear Regression Data for Compounds **15a-g**

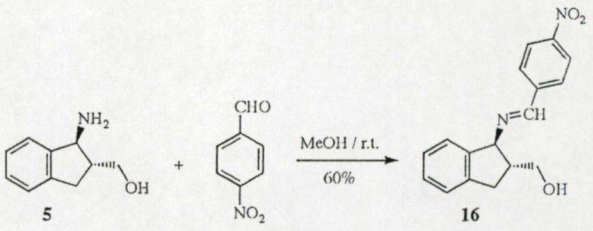
	B	**C**	[20]
Intercept	0.32	0.42	0.22
Slope	0.78	0.81	0.72
Corr. coeff	0.981	0.979	0.991
No. of points	7	7	6

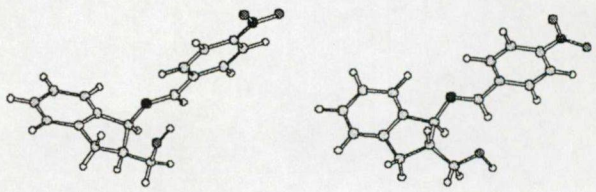
[20] The data for the corresponding cyclopentane-fused tetrahydro-1,3-oxazines

When the *trans*-amino alcohol **5** was condensed in methanol with *p*-nitrobenzaldehyde a well-defined product was obtained, which exists solely as the open, Schiff base form **16** (Scheme 4). In this case, the OH group is too far from the N=CH bond (4.5 Å), and intramolecular proton transfer is not possible without energy transfer (Figure 2).

When the *N*-benzylamino alcohol **6** was condensed with aldehydes in methanolic solution at room temperature only one diastereomer **17a-c** was observed in deuteriochloroform of the product at 300 K (Scheme 5). The product formed is stabilized by aromatic-aromatic interactions (Figure 3).

Scheme 4

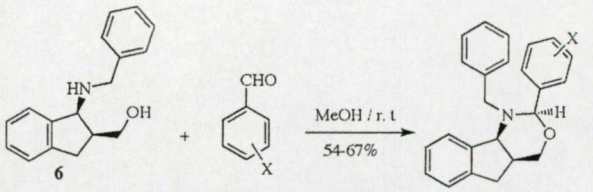




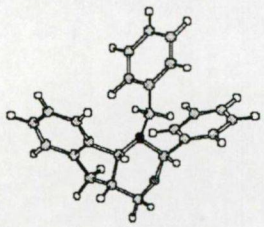
15Ad **16**

Figure 2. Stereoview of typical minimum energy molecular structures for **15Ad** and **16**.

Scheme 5



X = p-NO$_2$: **a**; H: **b**; p-NMe$_2$: **c**



17b

Figure 3. Stereoview of typical minimum energy molecular structure for **17b**.

EXPERIMENTAL

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60F$_{254}$ plates were used for TLC: the eluent was toluene–methanol 4:1. The ^{1}H- and ^{13}C nmr spectra were

recorded in deuteriochloroform solution in 5 mm tubes, at room temperature, on a Bruker *Avance* DRX 400 spectrometer at 400.13 (^{1}H) and 100.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. Compounds 1 and 2 were prepared by following literature methods [18].

Ethyl *cis*-1-Benzoylaminoindane-2-carboxylate (3).

Ethyl *cis*-2-aminoindane-1-carboxylate hydrochloride (4.84 g, 20 mmol) was allowed to react with benzoyl chloride (3.0 mL, 24 mmol) under Schotten-Baumann acylation conditions. After 2 h, the toluene phase was separated and dried (Na_2SO_4) and the solvent was evaporated off to yield a snow-white, crystalline product. Yield 5.18 g (84%), mp 151-153 °C (*n*-hexane); ^{1}H nmr (deuteriochloroform): δ 1.19 (3H, t, J = 7.1 Hz, $COOCH_2$-CH_3), 3.23 (1H, dd, J = 8.6, 16.4 Hz, 3-H), 3.41 (1H, dd, J = 5.8, 16.4 Hz, 3-H), 3.70 (1H, ddd, J = 5.8, 8.3 Hz, 2-H), 4.03-4.15 (2H, m, $COOCH_2$-CH_3), 6.05 (1H, t, J = 8.6 Hz, 1-H), 6.97 (1H, d, J = 9.1 Hz, 4'-H), 7.18-7.25 (2H, m, 3'-H, 5'-H), 7.33-7.53 (4H, m, 4-H, 5-H, 6-H, 7-H), 7.73-7.80 (2H, m, 2'-H, 6'-H); ^{13}C nmr (deuteriochloroform): δ 14.3, 34.8, 48.0, 55.6, 61.2, 124.7, 125.0, 127.2, 127.6, 128.7, 128.8, 131.9, 134.5, 141.1, 141.7, 167.1, 173.9.

Anal. Calcd. for $C_{19}H_{19}NO_3$ (309.37): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.47; H, 6.31; N, 4.71%.

General Procedure for Amino Alcohols 4-6.

To a slurry of $LiAlH_4$ (1.7 g, 45 mmol) in 50 mL of dry THF, amino ester 1 or 2 (3.07 g, 15 mmol) or N-benzoyl amino ester 3 (4.64 g, 15 mmol) in 20 mL of THF was added dropwise at 0 °C. After stirring and refluxing for 4 h (the end of the reduction was detected by means of TLC), the mixture was decomposed with 2 mL of water under ice cooling. The inorganic material was filtered off and washed with THF. After drying and evaporation, the resulting oils were crystallized from *n*-hexane and recrystallized from diisopropyl ether.

cis-1-Amino-2-hydroxymethylindane (4).

Compound 4 was obtained in 67 % yield (1.63 g), mp 83-84 °C, lit. mp [25]: 81-83 °C; ^{1}H nmr (deuteriochloroform): δ 2.67-2.97 (3H, m, 2-H, 2 x 3-H), 3.72-3.85 (2H, m, CH_2-OH), 4.59 (1H, d, J = 7.1 Hz, 1-H), 7.17-7.24 (3H, m, 4-H, 5-H, 6-H), 7.28-7.34 (1H, m, 7-H); ^{13}C nmr (deuteriochloroform): δ 33.3, 44.3, 58.6, 63.7, 124.0, 125.2, 127.1, 128.2, 141.8, 146.1.

Anal. Calcd. for $C_{10}H_{13}NO$ (163.22): C, 73.59; H, 8.03; N, 8.58. Found: C, 73.42; H, 8.21; N, 8.72%.

trans-1-Amino-2-hydroxymethylindane (5).

Compound 5 was obtained in 65% yield (1.59 g), mp 92-93 °C; ^{1}H nmr (deuteriochloroform): δ 2.27-2.39 (1H, m, 2-H), 2.52-2.58 (1H, m, 3-H), 2.94 (1H, dd, J = 8.1, 15.6 Hz, 3-H), 3.88-4.00 (2H, m, CH_2-OH), 4.17 (1H, d, J = 8.8 Hz, 1-H), 7.17-7.28 (4H, m, 4-H, 5-H, 6-H, 7-H); ^{13}C nmr (deuteriochloroform): δ 33.1, 52.7, 61.8, 66.4, 122.9, 124.9, 126.9, 127.6, 141.7, 146.9.

Anal. Calcd. for $C_{10}H_{13}NO$ (163.22): C, 73.59; H, 8.03; N, 8.58. Found: C, 73.51; H, 8.11; N, 8.61%.

cis-1-Benzylamino-2-hydroxymethylindane (6).

Compound 6 was obtained in 55% yield (2.09 g), mp 45-48 °C; ^{1}H nmr (deuteriochloroform): δ 2.68-2.78 (1H, m, 2-H), 2.87 (2H, d, J = 7.6 Hz, 2 x 3-H), 3.80 (1H, dd, J = 7.6, 11.6 Hz, CH_2-OH), 3.89 (1H, dd, J = 4.3, 11.6 Hz, CH_2-OH), 4.00 (2H, d, J = 2.8 Hz, NH-CH_2-Ph), 4.34 (1H, d, J = 7.1 Hz, 1-H), 7.17-7.30 (5H, m, Ph), 7.31-7.38 (4H, m, 4-H, 5-H, 6-H, 7-H); ^{13}C nmr (deuteriochloroform): δ 33.5, 44.4, 52.9, 63.6, 65.0, 124.2, 125.5, 126.8, 127.8, 128.3, 128.7, 128.9, 139.4, 143.3, 144.2.

Anal. Calcd. for $C_{17}H_{19}NO$ (253.35): C, 80.60; H, 7.56; N, 5.53. Found: C, 80.52; H, 7.31; N, 5.61%.

General Procedure for the Synthesis of 1,3-Oxazine-2-thiones 7 and 8.

Amino alcohol 4 (0.51 g, 3.16 mmol) or 6 (0.8 g, 3.16 mmol) in a solution (2 mL) of potassium hydroxide (0.22 g) was cooled to 0 °C, carbon disulfide (0.26 g) in dioxane (1.6 mL) was added and the mixture was stirred for 5 min. Potassium hydroxide (0.11 g) in water (2 mL) and then an aqueous solution (6 mL) of lead(II) nitrate (1.1 g) were added, followed by stirring at 60 °C for 10 min. The precipitated lead sulfide was filtered off, washed with hot water and extracted with hot ethanol. The aqueous filtrate and the ethanolic extracts were combined and evaporated to dryness. The crystalline product was recrystallized from diisopropyl ether–ethyl acetate.

cis-4,4a,5,9b-Tetrahydro-*1H*-indano[1,2-*d*][1,3]oxazine-2-thione (7).

Compound 7 was obtained in 62% yield (0.4 g), mp 160-161 °C; ^{1}H nmr (deuteriochloroform): δ 2.81 (1H, d, J = 16.1 Hz, 5-H), 2.96-3.07 (1H, m, 4a-H), 3.21 (1H, q, J = 7.8 Hz, 5-H), 3.88-3.98 (1H, m, 4-H), 4.41 (1H, dd, J = 4.8, 11.3 Hz, 4-H), 4.93 (1H, d, J = 7.1 Hz, 9b-H), 7.20-7.30 (3H, m, 6-H, 7-H, 8-H), 7.42-7.48 (1H, m, 9-H); ^{13}C nmr (deuteriochloroform): δ 32.9, 33.9, 58.9, 68.7, 125.1, 125.7, 127.9, 129.2, 139.9, 140.5, 187.8.

Anal. Calcd. for $C_{11}H_{11}NOS$ (205.28): C, 64.36; H, 5.40; N, 6.82. Found: C, 63.42; H, 5.51; N, 6.69%.

cis-1-Benzyl-4,4a,5,9b-tetrahydro-2-thioxo-*1H*-indano[1,2-*d*]-[1,3]oxazine (8).

Compound 8 was obtained in 56% yield (0.52 g), mp 133-137 °C; ^{1}H nmr (deuteriochloroform): δ 2.81-2.94 (2H, m, 4a-H, 5-H), 2.97-3.07 (1H, m, 5-H), 3.85 (1H, dd, J = 7.8, 11.6 Hz, 4-H), 3.93-4.01 (2H, m, 4-H, N-CH_2-Ph), 4.08 (1H, d, J = 12.8 Hz, N-CH_2-Ph), 4.67 (1H, d, J = 6.3 Hz, 9b-H), 7.20-7.40 (8H, m, Ph, 6-H, 7-H, 8-H), 7.48 (1H, d, J = 7.6 Hz, 9-H); ^{13}C nmr (deuteriochloroform): δ 33.3, 43.6, 49.5, 60.6, 63.7, 125.9, 126.6, 127.5, 129.4, 129.5, 129.9, 130.5, 131.0, 135.7, 144.6, 150.2.

Anal. Calcd. for $C_{18}H_{17}NOS$ (295.41): C, 73.19; H, 5.80; N, 4.74. Found: C, 73.32; H, 5.59; N, 4.85%.

cis-2-(4-Chlorophenyl)-4,4a,5,9b-tetrahydroindano[1,2-*d*][1,3]-oxazine (9).

Amino alcohol 4 (0.17 g, 1.02 mmol) and ethyl *p*-chlorobenzimidate (0.19 g, 1.02 mmol) were dissolved in toluene (20 mL), one drop of ethanol saturated with hydrogen chloride was added and the mixture was refluxed. The progress of the reaction was monitored by TLC. After the reaction was complete (6-8 h), the mixture was evaporated to dryness and the residue was recrystallized from diethyl ether. Yield 0.16 g (57%), mp 130-133 °C; ^{1}H nmr (deuteriochloroform): δ 2.67 (1H, dd, J = 2.0, 16.1 Hz, 5-H), 2.82-2.91 (1H, m, 4a-H), 3.20 (1H, dd, J = 7.6, 16.1 Hz, 5-H), 3.70 (1H, t, J = 10.6 Hz, 4-H), 4.30 (1H, dd, J = 5.5, 10.8 Hz, 4-H), 5.09 (1H, d, J = 6.6 Hz, 9b-H), 7.18-7.26 (3H, m, 6-H, 7-H, 8-H), 7.33 (2H, d, J = 8.6 Hz, 3'-H, 5'-H), 7.58 (1H, d, J = 6.8 Hz, 9-H), 7.90 (2H, d, J = 8.6 Hz, 2'-H, 6'-H); ^{13}C nmr (deuteriochloroform): δ 33.6, 34.6, 60.2, 65.9, 125.5, 125.9, 127.5, 128.1, 128.6, 129.2, 132.4, 136.6, 139.3, 146.1, 155.8

Anal. Calcd. for $C_{17}H_{14}ClNO$ (283.76): C, 71.96; H, 4.91; Cl, 12.49; N, 4.94. Found: C, 72.12; H, 5.13; Cl, 12.41; N, 4.78%.

General Synthesis for Thioureas **10** and **11**.

Amino alcohol **4** (0.81 g, 5 mmol) or **6** (1.25 g, 5 mmol) was dissolved in dry diethyl ether (20 mL) and a 10% excess of ethyl isothiocyanate was added (0.47 g, 5.5 mmol). The mixture was allowed to stand for 24 h at room temperature. After evaporation, the resulting crystalline thiourea adducts were recrystallyzed from diisopropyl ether.

cis-1-Ethyl-3-(2-hydroxymethylindan-1-yl)-thiourea (**10**).

Compound **10** was obtained in 85% yield (1.06 g), mp 164-166 °C; ^{1}H nmr (deuteriochloroform): δ 1.22 (3H, t, J = 7.3 Hz, NH-CH_2-CH_3), 2.67 (1H, q, J = 8.3, 3-H), 2.81 (1H, dd, J = 6.8, 13.4 Hz, 2-H), 2.95 (1H, q, J = 7.8 Hz, 3-H), 3.35 (2H, bs, NH-CH_2-CH_3), 3.70 (2H, d, J = 6.3 Hz, CH_2-OH), 5.95 (1H, d, J = 6.0 Hz, 1-H), 7.18-7.25 (3H, m, 4-H, 5-H, 6-H), 7.39 (1H, d, J = 6.8 Hz, 7-H); ^{13}C nmr (deuteriochloroform): δ 14.2, 33.5, 38.8, 46.3, 61.4, 62.6, 125.1, 125.4, 127.5, 128.9, 141.0, 143.5, 184.1.

Anal. Calcd. for $C_{13}H_{18}N_2OS$ (250.37): C, 62.37; H, 7.25; N, 11.19. Found: C, 62.22; H, 7.11; N, 11.25%.

cis-1-Benzyl-3-ethyl-1-(2-hydroxymethylindan-1-yl)-thiourea (**11**).

Compound **11** was obtained in 88% yield (1.49 g), mp 119-120 °C; ^{1}H nmr (deuteriochloroform): δ 0.94 (3H, t, J = 7.3 Hz, NH-CH_2-CH_3), 2.66 (1H, dd, J = 13.9, 19.1 Hz, 3-H), 2.94-3.09 (2H, m, 2-H, 3-H), 3.42-3.67 (3H, m, NH-CH_2-CH_3, CH_2-OH), 3.75 (1H, dd, J = 2.8, 11.6 Hz, CH_2-OH), 4.09 (1H, d, J = 15.6 Hz, N-CH_2-Ph), 4.28 (1H, d, J = 16.9 Hz, N-CH_2-Ph), 5.57 (1H, s, 1-H), 6.94-7.39 (9H, m, 4-H, 5-H, 6-H, 7-H, Ph); ^{13}C nmr (deuteriochloroform): δ 14.2, 35.1, 41.5, 47.8, 50.3, 62.4, 66.7, 125.2, 126.2, 127.0, 128.1, 2 x 129.0, 129.2, 134.9, 140.6, 144.3, 183.0.

Anal. Calcd. for $C_{20}H_{24}N_2OS$ (340.49): C, 70.55; H, 7.10; N, 8.23. Found: C, 70.29; H, 7.31; N, 8.45%.

General Procedure for 2-Ethyliminooxazines **12** and **13**.

Thiourea compound **10** (0.45 g, 1.8 mmol) or **11** (0.61 g, 1.8 mmol) was suspended in methanol (10 mL) and methyl iodide (1 mL) was added. After stirring at room temperature for 2 h, the reaction mixture was evaporated and the product was dissolved in 20 mL of dry THF. This solution was added dropwise to a suspension (55-65% oily dispersion) of NaH (0.7 g,) in 30 mL of dry THF under nitrogen. The reaction mixture was heated on an oil bath (60 °C) for 5 h, until no starting material could be observed by TLC. A few drops of water were carefully added to the reaction mixture in order to decompose the excess sodium hydride, and the solvent was evaporated off. Ice-cold water (25 mL) was added to the residue, which was then extracted with chloroform (3 x 40 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated off. The residue was crystallized from diethyl ether and recrystallized from *n*-hexane.

cis-2-Ethylimino-4,4a,5,9b-tetrahydro-1*H*-indano[1,2-*d*][1,3]-oxazine (**12**).

Compound **12** was obtained in 53% yield (0.22 g), mp 60-63 °C; ^{1}H nmr (deuteriochloroform): δ 1.13 (3H, t, J = 7.1 Hz, N-CH_2-CH_3), 2.58 (1H, dd, J = 2.0, 15.9 Hz, 4a-H), 2.72-2.82 (1H, m, 5-H), 3.09-3.25 (3H, m, 5-H, 2 x 4-H), 3.60 (1H, t, J = 10.3 Hz, N-CH_2-CH_3), 4.07 (1H, dd, J = 5.3, 10.3 Hz, N-CH_2-CH_3), 4.88 (1H, d, J = 6.8 Hz, 9b-H), 7.16-7.25 (3H, m, 6-H, 7-H, 8-H), 7.52 (1H, d, J = 7.3 Hz, 9-H); ^{13}C nmr (deuteriochloroform): δ 15.3, 33.3, 35.3, 36.4, 59.4, 66.0, 125.2, 125.5, 127.2, 127.4, 139.6, 146.3, 152.4.

Anal. Calcd. for $C_{13}H_{16}N_2O$ (216.29): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.27; H, 7.61; N, 12.75%.

cis-1-Benzyl-2-ethylimino-4,4a,5,9b-tetrahydro-1*H*-indano[1,2-*d*]-[1,3]oxazine (**13**).

Compound **13** was obtained in 55% yield (0.30 g), mp 77-81 °C; ^{1}H nmr (deuteriochloroform): δ 0.98 (3H, t, J = 7.1 Hz, N-CH_2-CH_3), 3.00-3.22 (5H, m, 2 x 4-H, 4a-H, 2 x 5-H), 4.08 (1H, dd, J = 2.5, 10.8 Hz, N-CH_2-CH_3), 4.23 (1H, d, J = 15.6 Hz, N-CH_2-Ph), 4.36 (1H, dd, J = 3.0, 10.8 Hz, N-CH_2-CH_3), 4.70 (1H, d, J = 8.8 Hz, N-CH_2-Ph), 5.24 (1H, d, J = 15.4 Hz, 9b-H), 7.13-7.25 (3H, m, 6-H, 7-H, 8-H), 7.27-7.45 (6H, m, 9-H, Ph), ^{13}C nmr (deuteriochloroform): δ 17.0, 34.6, 38.7, 39.9, 50.8, 61.0, 67.3, 125.3, 125.6, 126.8, 127.3, 128.3, 128.6, 128.8, 138.3, 141.6, 142.8, 152.4.

Anal. Calcd. for $C_{20}H_{22}N_2O$ (306.48): C, 78.40; H, 7.24; N, 9.14. Found: C, 78.52; H, 7.52; N, 9.35%.

cis-2-Ethylimino-4,4a,5,9b-tetrahydro-1*H*-indano[1,2-*d*][1,3]thiazine (**14**).

Thiourea **10** (0.63 g, 2.5 mmol) was refluxed for 1 h in ethanol (25 mL) containing 10% dry hydrogen chloride. The solvent was evaporated off, and the residue was neutralized with 10% aqueous sodium carbonate and extracted with chloroform (3 x 30 mL). After drying and evaporation off the organic solution, a crystalline product was obtained, which was recrystallized from methanol–diisopropyl ether. Yield 0.35 g (60%), mp 82-84 °C; ^{1}H nmr (deuteriochloroform): δ 1.17 (3H, t, J = 7.3 Hz, N-CH_2-CH_3) 2.69-2.81 (4H, m, 4-H, 4a-H, 2 x 5-H), 3.17-3.45 (3H, m, 4-H, N-CH_2-CH_3), 5.14 (1H, d, J = 6.3 Hz, 9b-H), 7.16-7.24 (3H, m, 6-H, 7-H, 8-H), 7.50 (1H, d, J = 7.1 Hz, 9-H), ^{13}C nmr

Table 3

Physical Data on Compounds **15a-g**

Comp.	M.p. (°C)	Yield (%)	Formula	M.W. chain (A)	δN=C*H*Ar ring (B)	δN-C*H*Ar-N ring (C)	δN-C*H*Ar-N
15a	113-115	61	$C_{17}H_{16}N_2O_3$	296.33	8.53	5.25	5.10
15b	oil	~100	$C_{17}H_{16}BrNO$	330.23	8.37	5.14	4.99
15c	71-74	51	$C_{17}H_{16}ClNO$	285.78	8.39	5.14	4.70
15d	83-87	58	$C_{17}H_{17}NO$	251.33	8.45	5.18	5.03
15e	73-76	52	$C_{18}H_{19}NO$	265.36	8.39	5.14	4.99
15f	103-106	50	$C_{18}H_{19}NO_2$	281.36	8.37	5.13	4.98
15g	129-133	62	$C_{19}H_{22}N_2O$	294.40	8.30	5.05	4.90

(deuteriochloroform); δ 15.1, 29.0, 36.0, 37.3, 37.4, 63.3, 125.0, 125.3, 126.9, 127.4, 139.6, 146.1, 148.5.

Anal. Calcd. For $C_{13}H_{16}N_2S$ (232.35): C, 67.20; H, 6.94; N, 12.06. Found: C, 67.37; H, 7.01; N, 12.22%.

General Procedure for the Reactions of Amino Alcohols with Aromatic Aldehydes to form **15a-g, 16, 17a-c.**

To a solution of the appropriate amino alcohol **4-6** (1.2 mmol) in 20 mL of absolute methanol, an equivalent amount of aromatic aldehyde was added (liquid aldehydes were freshly distilled), and the mixture was allowed to stand at ambient temperature for 1 day. The solvent was then evaporated off and the evaporation was repeated after the addition of 10 mL of benzene. The crystalline products were collected by filtration and recrystallized from diisopropyl ether–ethyl acetate. The oily product **15b** was dried in a vacuum desiccator for 24 h.

trans-1-(4-Nitrobenzylideneamino)indane-2-methanol (**16**).

Compound **16** was obtained in 60% yield (0.21 g), mp 133-134 °C; ^{1}H nmr (deuteriochloroform): δ 2.83-2.92 (2H, m, 2 x 3-H), 3.20-3.31 (1H, m, 2-H), 3.78-3.88 (2H, m, C*H*$_2$-OH), 4.88 (1H, d, J = 6.3 Hz, 1-H), 7.02 (1H, d, J = 7.6 Hz, 4-H), 7.17-7.32 (3H, m, 5-H, 6-H, 7-H), 7.97 (2H, d, J = 8.8 Hz, 2'-H, 6'-H), 8.27 (2H, d J = 8.6 Hz, 3'-H, 5'-H), 8.55 (1H, s, N=C*H*); ^{13}C nmr (deuteriochloroform): δ 34.3, 50.1, 64.3, 77.4, 124.0, 124.5, 125.3, 126.9, 128.3, 129.3, 141.7, 142.5, 143.0, 149.3, 159.3.

Anal. Calcd. For $C_{17}H_{16}N_2O_3$ (296.33): C, 68.91; H, 5.44; N, 9.45. Found: C, 68.67; H, 5.21; N, 9.22%.

(2*R**,4a*S**,9b*S**)-1-Benzyl-2-(4-nitrophenyl)-1,2,4,4a,5,9b-hexahydroindano[1,2-*d*][1,3]oxazine (**17a**).

Compound **17a** was obtained in 67% yield (0.31 g), mp 164-166 °C; ^{1}H nmr (deuteriochloroform): δ 2.36 (1H, d, J = 15.9 Hz, 4a-H), 2.84 (1H, dd, J = 6.0, 15.6 Hz, 5-H), 3.00-3.09 (1H, m, 5-H), 3.48 (1H, t, J = 11.6 Hz, N-C*H*$_2$-Ph), 3.68 (1H, d, J = 14.6 Hz, 4-H), 3.86 (1H, d, J = 14.6 Hz, 4-H), 4.26 (1H, dd, J = 7.1, 11.6 Hz, N-C*H*$_2$-Ph), 4.49 (1H, d, J = 6.0 Hz, 9b-H), 5.49 (1H, s, 2-H), 7.17-7.24 (3H, m, 6-H, 7-H, 8-H), 7.26-7.34 (3H, m, 9-H, Ph), 7.40 (2H, d, J = 7.6 Hz, Ph), 7.62 (1H, d, J = 7.6 Hz, Ph), 7.77 (2H, d, J = 8.56 Hz, 2'-H, 6'-H), 8.21 (2H, d, J = 8.8 Hz, 3'-H, 5'-H); ^{13}C nmr (deuteriochloroform): δ 30.3, 33.2, 50.8, 64.5, 69.9, 87.1, 123.6, 124.2, 126.0, 127.3, 127.4, 127.5, 128.0, 128.1, 128.6, 129.6, 141.7, 142.0, 147.1, 147.7.

Anal. Calcd. For $C_{24}H_{22}N_2O_3$ (386.45): C, 74.59; H, 5.74; N, 7.25. Found: C, 74.71; H, 5.62; N, 7.42%.

(2*R**,4a*S**,9b*S**)-1-Benzyl-2-phenyl-1,2,4,4a,5,9b-hexahydroindano[1,2-*d*][1,3]oxazine (**17b**).

Compound **17b** was obtained in 54% yield (0.22 g), mp 117-119 °C; ^{1}H nmr (deuteriochloroform): δ 2.33 (1H, d, J = 15.9 Hz, 4a-H), 2.81 (1H, dd, J = 6.6, 16.1 Hz, 5-H), 2.97-3.07 (1H, m, 5-H), 3.46 (1H, t, J = 11.6 Hz, N-C*H*$_2$-Ph), 3.81 (1H, d, J = 14.6 Hz, 4-H), 3.86 (1H, d, J = 15.1 Hz, 4-H), 4.23 (1H, dd, J = 7.6, 11.8 Hz, N-C*H*$_2$-Ph), 4.45 (1H, d, J = 6.3 Hz, 9b-H), 5.45 (1H, s, 2-H), 7.14-7.38 (9H, m, 6-H, 7-H, 8-H, 9-H, Ph), 7.43 (2H, d, J = 8.1 Hz, 3'-H, 5'-H), 7.56 (2H, d, J = 7.6 Hz, 2'-H, 6'-H), 7.63 (1H, d, J = 7.3 Hz, 4'-H); ^{13}C nmr (deuteriochloroform): δ 30.4, 33.2, 50.5, 64.3, 69.9, 87.8, 124.4, 125.8, 126.4, 126.9, 127.2, 127.6, 127.7, 128.2, 128.4, 128.5, 139.7, 140.5, 141.7, 142.6.

Anal. Calcd. For $C_{24}H_{23}NO$ (341.46): C, 84.42; H, 6.79; N, 4.10. Found: C, 84.37; H, 6.91; N, 4.22%.

(2*R**,4a*S**,9b*S**)-1-Benzyl-2(4-dimethylaminophenyl)-1,2,4,4a,5,9b-hexahydroindano[1,2-*d*][1,3]oxazin (**17c**).

Compound **17c** was obtained in 59% yield (0.27 g), mp 205-207 °C; ^{1}H nmr (deuteriochloroform): δ 2.32 (1H, d, J = 15.6 Hz, 4a-H), 2.80 (1H, dd, J = 6.6, 17.1 Hz, 5-H), 2.92 (6H, s, N*Me*$_2$) 2.97-3.03 (1H, m, 5-H), 3.45 (1H, t, J = 11.6 Hz, N-C*H*$_2$-Ph), 3.78 (1H, d, J = 14.9 Hz, 4-H), 3.94 (1H, d, J = 14.9 Hz, 4-H), 4.20 (1H, dd, J = 6.6, 11.3 Hz, N-C*H*$_2$-Ph), 4.43 (1H, d, J = 5.5 Hz, 9b-H), 5.39 (1H, s, 2-H), 7.08-7.65 (13H, m, 6-H, 7-H, 8-H, 9-H, 2'-H, 3'-H, 5'-H, 6'-H, Ph); ^{13}C nmr (deuteriochloroform): δ 30.6, 33.4, 41.1, 50.5, 64.4, 70.0, 88.1, 112.8, 124.6, 125.9, 2 x 127.0, 127.3, 127.7, 128.4, 128.6, 141.0, 141.9, 143.0, 149.3, 154.2.

Anal. Calcd. For $C_{26}H_{28}N_2O$ (384.53): C, 81.21; H, 7.34; N, 7.29. Found: C, 81.34; H, 7.05; N, 7.42%.

Acknowledgements.

The authors thank Ms. Blanka Tóth for her kind assistance in part of the synthesis. Their thanks are also due to the Hungarian Research Foundation (OTKA TS 04888 and T 034901) for financial support.

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VI.

Facile Regio- and Diastereoselective Syntheses of Hydroxylated 2-Aminocyclohexanecarboxylic acids

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Keywords: Amino acids / Heterocycles / Diastereoselectivity / Structure elucidation

By means of total regio- and diastereoselective functionalizations of *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acid derivatives **1, 9, 12** and **16**, isomers of 2-amino-4-hydroxycyclohexanecarboxylic acid **8** and **11,** and 2-amino-5-hydroxycyclohexanecarboxylic acid **15** and **19** were prepared in good yields, via 1,3-oxazine or γ-lactone intermediates. The enantiomers of **8** and **15** were also prepared by the same pathway, resulting in the products with ee > 99%. The structures, stereochemistry and relative configurations of the synthetized compounds were proved by NMR, using some key vicinal couplings and characteristic NOEs.

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Introduction

The continuously increasing interest in cyclic β-amino acids[1-3] is mainly connected with the importance of the naturally-occurring cispentacin,[4] which exerts strong anticandida activity. A further feature is the fact that Gellman's group recently synthetized and investigated[5] *trans*-2-aminocyclopentane- and *trans*-2-aminocyclohexanecarboxylic acid oligomers, which clearly display a stable helical conformation. We have found that by inversion of the relative configurations of the *cis* oligomers, the preferred conformation can be switched from a helix to a single non-polar strand.[6] Cyclic β-amino acids are widely used as starting substances for the preparation of heterocycles. Through their incorporation in place of an α-amino acid of a naturally-occurring pharmacologically active peptide, the activity or the effect can be modified and the stabilities of the natural peptides can be increased. Changes of the configuration and differences in the ring size allow modification of the conformations of the peptides. They are also applicable in combinatorial syntheses.[7-10]

In recent years, a number of new syntheses of functionalized derivatives have been reported (see *e.g.* ref. [11]). Among them, hydroxy-substituted β-amino acids are of considerable importance because of their occurrence in many biologically active compounds (*e.g.* taxol and related molecules).[2,7] Our present aim was to introduce an extra hydroxy group at position 4 or 5 of the cyclohexane ring. For these syntheses, the readily available *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acids were used. For the derivatization, we considered two strategies: cyclization on an acylamino derivative via 1,3-oxazine formation, or cyclization on a carboxylic acid function via lactone formation (iodolactonization protocol).

Results and discussion

The starting *cis*-2-amino-4-cyclohexenecarboxylic acid was prepared by hypochlorite-mediated Hoffman degradation of the carboxamide obtained by ammonolysis of *cis*-1,2,3,6-tetrahydrophthalic anhydride.[12] The amino acid was esterified in the presence of ethanol and thionyl chloride than acylated with *tert*-butoxy pyrocarbonate, acetic anhydride or benzoyl chloride, resulting in *N*-acylated amino esters **1a-c**, respectively.

With *N*-iodo- (NIS) or *N*-bromosuccinimide (NBS) (for a related transformation, see *e.g.* ref. [13]), the *N*-Boc derivative **1c** gave oxazinone **2**, while the *N*-acetyl and *N*-benzoyl derivatives **1a** and **1b** furnished the corresponding methyl- or phenyl-substituted oxazines **5a,b** and **6a,b** regio- and diastereoselectively (Scheme 1). Not even traces of other regio- or diastereomers were observed in the crude product. Iodooxazinone **2** and bromooxazine

derivatives **5a,b** and **6a,b** were dehalogenated with tributyltin hydride under an argon atmosphere, resulting in compounds **3** and **7a,b**, respectively. Acidic hydrolysis of **3** gave the stable oxazinonecarboxylic acid derivative **4**, which slowly decomposed on further heating. Hydrolysis of oxazines **7a,b** with 20% aqeous HCl, and removal of the HCl by ion-exchange chromatography led to the *all-cis* isomer of 2-amino-4-hydroxycyclohexanecarboxylic acid **8** (Scheme 1).

Insert Scheme 1

The corresponding *trans*-2-amino-4-cyclohexenecarboxylic acid was prepared by Hoffman degradation of the carboxamide obtained by ammonolysis of *trans*-1,2,3,6-tetrahydrophthalic anhydride. The amino acid was esterified, and subsequent treatment with acetic anhydride resulted in *N*-acetylamino ester **9**. By a similar transformation as for the *cis* isomer **1a**, the *trans*-2-acetylamino-4-cyclohexenecarboxylic acid **9** reacted via the iodooxazine intermediate **10** to furnish the corresponding (*r*-1,*t*-2,*t*-4)-2-amino-4-hydroxycyclohexanecarboxylic acid **11** (Scheme 2).

Insert Scheme 2

Stereoselective iodolactonization[7] was the key step in the synthesis of 2-amino-5-hydroxycyclohexanecarboxylic acid. The reactions of *N*-benzoyl- and *N*-Boc-protected *cis*-2-amino-4-cyclohexenecarboxylic acid **12a,b** with I_2/KI in slightly alkaline medium yielded iodolactones **13a,b** in fairly good yields, with excellent regio- and diastereoselectivity; the products were reduced with tributyltin hydride to give lactones **14a,b**. The acidic hydrolysis of benzoyl derivative **14a** did not give the desired amino acid; instead, decomposition took place. When the *N*-Boc lactone **14b** was hydrolysed after ion exchange chromatography, the *all-cis* isomer of 2-amino-5-hydroxycyclohexanecarboxylic acid **15** was obtained in 66% yield (Scheme 3).

Insert Scheme 3

By a similar transformation, from *trans*-2-*tert*-butoxycarbonylamino-4-cyclohexenecarboxylic acid **16** via iodolactone **17**, the corresponding (*r*-1,*t*-2,*c*-5)-2-amino-5-hydroxycyclohexanecarboxylic acid **19** was prepared (Scheme 4).

Insert Scheme 4

The enantiomeric *cis* compounds (+)-**8** and (-)-**15** were synthetized from *rac*-7-azabicyclo[4.2.0]oct-3-en-8-one by CAL-B treatment with one equivalent of H_2O in isopropyl ether, as described earlier.[14] The enantiopure β-lactam obtained was transformed with 18% HCl into the (1*S*,2*R*)-2-amino-4-cyclohexenecarboxylic acid hydrochloride.[14] The syntheses of the 4-hydroxy- and 5-hydroxyamino acid enantiomers (+)-**8** and (-)-**15** were carried out similarly as for the racemic compounds given in Schemes 1 and 3, resulting in the products with ee > 99%.

The given stereochemistry and the relative configurations of the synthetized compounds were proved by using some key vicinal couplings and characteristic NOEs. For **8**, there is a low ^3J(H-1,H-2) = 4.1 Hz and a high ^3J(H-1,H-6ax) = 13.6 Hz, demonstrating an *axial* H-1 and an *equatorial* H-2. Unfortunately, the coupling pattern of the H-4 signal could not be resolved, but H-3*ax* exhibits only a single large coupling of 12.6 Hz, stemming from the geminal H-3*eq*. This suggests an *equatorial* H-4, which, together with the very probable chair ring conformation, proves the relative stereochemistry.

For compound **11**, H-2 has two large vicinal coupling constants (^3J = 10.8 and 12.1 Hz), indicating its *diaxial* position relative to H-3*ax* and H-1. *Axial* H-4 is supported by the NOE interaction observed between H-4 and H-2, showing that the NH_2 and the OH are situated on the same side of the ring.

In compound **15**, the *cis* orientation of the *equatorial* amino and the *axial* carboxyl group can readily be concluded from the low coupling constants observed for H-2 and the single large coupling of 12.1 Hz for H-1. The *axial* position of H-5 can be seen from the multiple large couplings for H-6*ax* (1.61 ppm). The NOE interaction between H-5 and H-1 reinforces the *cis* stereochemistry of the OH and the carboxyl groups.

The two large couplings for H-2 point to its *trans-diaxial* orientation relative to H-1 and H-3 in **19**. There are two large vicinal couplings for H-5 too, confirming the *equatorial* arrangement of the OH group. The NOE observed between H-5 and H-1 corroborates their identical orientation relative to the ring.

X-Ray diffraction studies confirmed the structure of **15**. All bonding parameters are in the usual ranges. The molecular structure and extensive hydrogen bonding system of **15** is presented in Figure 1.

Insert Figure 1

Experimental Section

General Procedures: ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz in $CDCl_3$ or in DMSO-(D6), at ambient temperature, on a Bruker AM 400 spectrometer. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$ or DMSO) as internal standards. Elemental analyses were performed with a Perkin-Elmer CHNS-2400 Ser II Elemental Analyzer. Melting points were measured on a Kofler melting point apparatus and are uncorrected.

The ee values of the synthetized enantiomers were determined by gas chromatography (GC) on a Chromopak Chiralsil-Dex CB (CCD) or Chirasil-L-Val (CLV) columns. (1*S*,2*R*)-Ethyl 2-amino-4-cyclohexenecarboxylate: CCD column, after derivatization with acetic anhydride in the presence of 4-dimethylaminopyridine and pyridine [120 °C for 2 min → 190 °C (rate of temperature rise 10 °C/min; 100 kPa), retention time (min): 10.86 (antipode: 10.77)]; **(+)-1a** and **(+)-14b**: CCD column, 120 °C for 2 min → 190 °C (rate of temperature rise 10 °C/min; 100 kPa), retention times (min) **(+)-1a**: 10.86 (antipode: 10.77), **(+)-14b**: 17.48 (antipode: 17.19); **(+)-12b**: CLV column, after derivatization with diazomethane, 100 °C for 10 min → 160 °C (rate of temperature rise 10 °C/min; 45 kPa), retention time **(+)-12b**: 26.61 (antipode: 26.49). The ee values of **(+)-8** and **(-)-15** were determined on a CCD column after double derivatization with (*i*) diazomethane; (*ii*) acetic anhydride in the presence of 4-dimethylaminopyridine and pyridine [120 °C for 2 min → 190 °C (rate of temperature rise 10 °C/min; 100 kPa), retention times (min): **(+)-8**: 20.17 (antipode: 19.59); (-)-15: 18.34 (antipode: 17.82)].

Ethyl *cis*-2-(*tert*-butoxycarbonylamino)-4-cyclohexenecarboxylate (1a): Ethyl *cis*-2-amino-4-cyclohexenecarboxylate hydrochloride (2.04 g, 10 mmol) was dissolved in a mixture of toluene (25 mL) and 1 M NaOH solution (25 mL), and *tert*-butoxypyrocarbonate (2.4 g, 11 mmol) was them added with stirring. Stirring was continued for 1 h, after which the toluene layer was separated off, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried (Na_2SO_4) and evaporated. The residue was recrystallized from *n*-hexane—diisopropyl ether: a white solid (1.63 g, 61% yield), mp 70-72 °C; ^{1}H NMR (DMSO) δ 1.17 (*t*, J = 7.0 Hz, 3H, CH_3CH_2), 1.37 (*s*, 9H, OtBu), 2.02 (*d*, J = 17.9 Hz, 1H, H-5), 2.13 (*d*, J = 17.9 Hz, 1H, H-2), 2.27 (*d*, J = 17.9 Hz, 1H, H-5), 2.41 (*d*, J = 17.9 Hz, 1H, H-2), 2.74-2.80 (*m*, 1H, H-1), 3.94-4.11 (*m*, H-6, 3H, CH_3CH_2), 5.54 (*d*, J = 10.4 Hz, 1H, H-4), 5.61 (*d*, J = 10.4 Hz, 1H, H-3), 6.49 (*d*, J = 8.3 Hz, 1H, NH); ^{13}C NMR

(DMSO) δ 14.4, 24.1, 28.5, 30.7, 41.4, 46.1, 60.1, 78.0, 124.4, 125.4, 155.4, 172.9. Anal. Calcd. for $C_{14}H_{23}NO_4$ (269.35): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.84; H, 8.32; N, 5.55.

Ethyl *cis*-2-acetylamino-4-cyclohexenecarboxylate (1b): To a suspension of ethyl *cis*-2-amino-4-cyclohexenecarboxylate hydrochloride (2.04 g, 10 mmol) in toluene (40 mL), triethylamine (2.04 g, 20 mmol) and acetyl chloride (0.94 g, 12 mmol) were added, and the mixture was stirred at room temperature for 2 h, and washed with water (2 x 10 mL). The aqueous layer was extracted with *n*-hexane (3 x 20 mL). The combined organic phase was dried (Na_2SO_4) and evaporated. The residue was recrystallized from *n*-hexane—diisopropyl ether: a white solid (1.15 g, 55% yield), mp 64-67 °C; ^{1}H NMR (DMSO) δ 1.14 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.77 (s, 3H, COCH_3), 2.00 (d, J = 17.6 Hz, 1H, H-5), 2.15 (d, J = 18.6 Hz, 1H, H-2), 2.27 (d, J = 17.6 Hz, 1H, H-5), 2.71-2.76 (m, 1H, H-2), 4.28-4.34 (m, 1H, H-6), 5.56 (d, J = 10.3 Hz, 1H, H-4), 5.64 (d, J = 10.3 Hz, 1H, H-3), 7.59 (d, J = 7.6 Hz, 1H, NH); ^{13}C NMR (DMSO) δ 14.9, 23.4, 24.6, 31.1, 41.8, 44.8, 60.6, 125.9, 125.1, 169.8, 173.4. Anal. Calcd. for $C_{11}H_{17}NO_3$ (211.26): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.24; H, 7.82; N, 6.48.

Ethyl *cis*-2-benzoylamino-4-cyclohexenecarboxylate (1c): Ethyl *cis*-2-amino-4-cyclohexenecarboxylate hydrochloride (2.04 g, 10 mmol) was benzoylated according to the Schotten-Baumann method. After separation, drying and evaporation of the toluene layer, an almost white crystalline product was obtained. After recrystallization from *n*-hexane—EtOAc, a white crystalline product, 1.76 g (65%), was obtained. Mp 105-106 °C; ^{1}H NMR (DMSO) δ 1.13 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 2.30-2.40 (m, 3H, H-2, H-5), 2.47 (s, 1H, H-2), 2.93-2.99 (m, 1H, H-1), 3.97-4.1 (m, 2H, CH$_3$CH_2), 4.43-4.50 (m, 1H, H-6), 5.65 (q, J = 9.8 Hz, 2H, H-3, H-4), 7.44 (t, J = 7.3 Hz, 2H, *m*-Ph), 7.52 (t, J = 7.3 Hz, 1H, *p*-Ph), 7.78 (d, J = 7.3 Hz, 2H, *o*-Ph), 8.00 (d, J = 7.5 Hz, 1H, NH); ^{13}C NMR (DMSO) δ 14.4, 25.1, 29.5, 41.3, 45.6, 60.2, 124.8, 125.3, 127.8, 128.4, 131.4, 135.1, 166.7, 173.0. Anal. Calcd. for $C_{16}H_{19}NO_3$ (273.34): C, 70.31; H,7.01; N, 5.12. Found: C, 70.44; H, 7.27; N, 5.48.

Ethyl *trans*-2-acetylamino-4-cyclohexenecarboxylate (9): Starting from ethyl *trans*-2-amino-4-cyclohexenecarboxylate hydrochloride, the procedure described for **1b** was followed to prepare **9:** yield 58%, white solid, mp 68-69 °C; ^{1}H NMR (DMSO) δ 1.16 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.76 (s, 3H, COCH$_3$), 1.87-1.98 (m, 1H, H-5), 2.19 (dt, J = 17.1, 4.3 Hz, 1H, H-5), 2.25-2.29 (m, 2H, H-2, H-1), 2.55 (dt, J = 10.1, 7.5 Hz, 1H, H-2), 4.11-4.19 (m, CH$_3$CH_2, 3H, H-6), 5.56-5.66 (m, 2H, H-3, H-4), 7.85 (d, J = 8.3 Hz, 1H, N*H*); ^{13}C NMR (DMSO) δ 14.4, 23.0, 27.6, 31.1, 44.6, 45.9, 60.2, 125.2, 125.1, 168.7, 173.6. Anal. Calcd. for $C_{11}H_{17}NO_3$ (211.26): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.63; H, 8.42; N, 6.91.

General procedure for the synthesis of iodo- and bromooxazines (2, 5a,b, 6a,b and 10): A solution of *N*-acylamino ester **1a-c** or **9** (3 mmol) in CH_2Cl_2 (40 mL) was treated with equivalent of NIS or NBS, and the reaction mixture was stirred for 14 h at rt. When the reaction was completed (monitored by TLC), the mixture was treated with 10% aqueous NaOH solution (3 x 20 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 40 mL), and the combined organic layer was dried (Na_2SO_4) and evaporated. The residue was recrystallized from *n*-hexane–diisopropyl ether.

2: Yield 80%, a white crystalline solid, mp 199-201 °C; ^{1}H NMR (DMSO) δ 1.21 (t, J = 7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.95 (ddt, J = 1.8, 14.1, 4.0 Hz, 1H, H-9eq), 2.00-2.16 (m, 2H, H-7), 2.55 (d, J = 14.1 Hz, 1H, H-9ax), 2.85 (ddd, J = 1.5, 5.5, 11.1 Hz, 1H, H-6), 3.81 (br s, 1H, H-5), 4.01-4.16 (m, 2H, CH$_3$C*H*$_2$), 4.58-4.63 (m, 1H, H-1), 4.73-4.79 (m, 1H, H-8), 7.69 (d, J = 5.0 Hz, 1H, H-4); ^{13}C NMR (DMSO) δ 14.3, 25.3, 28.1, 28.7, 43.1, 46.6, 60.9, 75.4, 152.6, 171.6. Anal. Calcd. for $C_{10}H_{14}INO_4$ (339.13): C, 35.42; H, 4.16; N, 4,13. Found: C, 35.13; H, 4.27; N, 3.98.

5a: This compound was very sensitive to air, and was used in the dehalogenation step without further purification.

5b: Yield 80%, a white crystalline solid, mp 113-114 °C; ^{1}H NMR (DMSO) δ 1.21 (t, J = 7.05 Hz, 3H, C*H*$_3$CH$_2$), 1.83-1.96 (m, 2H, H-7, H-9), 2.04 (d, J = 3.2 Hz, 1H, H-7), 2.62 (dt, J = 14.1, 1.3 Hz, 1H, H-9), 3.04 (ddd, J = 3.0, 4.0, 12.3 Hz, 1H, H-6), 4.12 (q, J = 7.3 Hz, 2H, CH$_3$C*H*$_2$), 4.16-4.20 (m, 1H, H-6), 4.74-4.78 (m, 1H, H-1), 4.85-4.89 (m, 1H, H-8), 7.41 (t, J = 7.8 Hz, 2H, *m*-Ph), 7.48 (t, J = 7.0 Hz, 1H, *p*-Ph), 7.81 (d, J = 8.1 Hz, 2H, *o*-Ph); ^{13}C NMR (DMSO) δ 14.4, 24.4, 29.0, 29.3, 42.9, 48.8, 60.6, 73.3, 127.2, 128.5, 131.2, 132.8, 155.9, 172.0. Anal. Calcd for $C_{16}H_{18}INO_3$ (399.23): C, 48.14; H, 4.54; N, 3.51. Found: C, 47.89; H, 4.32; N, 3.87.

6a: Yield 83%, a white crystalline solid, mp 68-69 °C; ^{1}H NMR (DMSO) δ 1.22 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$), 1.70 (ddt, J = 1.5, 13.8, 4.0 Hz, 1H, H-9), 1.86 (s, 3H, Me-3), 1.99-2.05 (m, 2H, H-7), 2.35 (dt, J = 13.8, 1.5 Hz, 1H, H-9), 2.93 (ddd, J = 2.8, 6.0, 10.3 Hz, 1H, H-6), 3.89-3.94 (m, 1H, H-5), 4.00-4.15 (m, 2H, CH$_3$C*H*$_2$), 4.48-4.52 (m, 1H, H-1), 4.64-4.68 (m, 1H, H-8); ^{13}C NMR (DMSO) δ 16.8, 23.6, 29.5, 38.6, 45.3, 61.7, 63.7, 64.5, 74.9, 172.7, 174.2. Anal. Calcd for $C_{11}H_{16}BrNO_3$ (290.17): C, 45.53; H,5.56; N, 4.83. Found: C, 45.89; H, 5.72; N, 4.37.

6b: Yield 81%, a white crystalline solid, mp. 119-120 °C; ^{1}H NMR (DMSO) δ 1.22 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.86 (ddt, J = 1.5, 13.8, 3.8 Hz, 1H, H-9), 1.95-2.13 (m, 2H, H-7), 2.49 (dt, J = 10.3, 1.5 Hz, 1H, H-9), 3.07 (ddd, J = 2.8, 4.3, 11.8 Hz, 1H, H-6), 4.13 (q, J = 7.0 Hz, 2H, CH$_3$CH_2), 4.20-4.24 (m, 1H, H-5), 4.47-4.78 (m, 1H, H-1), 4.78-4.83 (m, 1H, H-8), 7.41 (t, J = 7.55 Hz, 2H, *m*-Ph), 7.49 (t, J = 7.3 Hz, 1H, *p*-Ph), 7.81 (d, J = 7.3 Hz, 2H, *o*-Ph); ^{13}C NMR (DMSO) δ 14.4, 23.3, 27.6, 42.4, 48.6, 49.9, 60.6, 72.2, 127.2, 128.5, 131.2, 132.9, 155.6, 172.1. Anal. Calcd for $C_{11}H_{18}BrNO_3$ (252.24): C, 54.56; H, 5.15; N, 3.98. Found: C, 54.41; H, 5.49; N, 4.22.

10: This compound is sensitive to air, and was used for the next step without purification. ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.64 (d, J = 14.1 Hz, 1H, H-9), 1.90 (s, 3H, Me), 2.24 (ddd, J = 3.5, 7.3, 16.4 Hz, 1H, H-7), 2.44 (d, J = 16.4 Hz, 1H, H-7), 2.53 (d, J = 14.1 Hz, 1H, H-9), 2.73 (d, J = 6.1 Hz, 1H, H-6), 3.83 (s, 1H, H-5), 4.11 (q, J = 7.0 Hz, 2H, CH$_3$CH_2), 4.52 (s, 1H, H-1), 4.53 (s, 1H, H-8); ^{13}C NMR (DMSO) δ 14.8, 20.5, 21.6, 27.5, 41.1, 46.3, 49.5, 61.1, 72.9, 158.9, 172.8.

General procedure for dehalogenation of iodo- and bromooxazines 2, 5a,b, 6a,b and 10 to oxazines 3, 7a and 7: Tributyltin hydride (0.8 mL, 3 mmol) was added to a solution of iodo- or bromooxazine **2**, **5a,b** or **6a,b** (1.48 mmol) in dry CH_2Cl_2 (65 mL) under an argon atmosphere. After stirring for 20 h at 40 °C, the solvent was evaporated off and the residue was purified by column chromatography on silica gel (eluent: *n*-hexane–EtOAc 10:1) to afford the 1,3-oxazine as a white crystalline solid (**3**, **7b**) or as an oil (**7a**).

3: Yield 70%, a white crystalline solid, mp 150-153 °C; ^{1}H NMR (DMSO) δ 1.20 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 1.53-1.66 (m, 2H, H-7, H-8), 1.71-1.78 (m, 1H, H-8), 1.86-1.91 (m, 2H, H-9), 1.91-1.97 (m, 1H, H-7), 2.65 (ddd, J = 2.0, 4.5, 11.8 Hz, 1H, H-6), 3.79 (br s, 1H, H-5), 4.00-4.13 (m, 2H, CH$_3$CH_2), 4.49-4.55 (m, 1H, H-1), 7.37 (d, J = 5.0 Hz, 1H, H-4); ^{13}C NMR (DMSO) δ 14.8, 18.7, 29.5, 30.9, 46.5, 47.4, 60.1, 72.6, 154.3, 173.1. Anal. Calcd for $C_{10}H_{15}NO_4$ (213.24): C, 56.33; H, 7.09; N, 6.57. Found: C, 55.92; H, 7.22; N, 6.19.

7a: Yield 60%, a colourless oil, from iodooxazine **5a**, and 55% from bromooxazine **5b**; ^{1}H NMR (DMSO) δ 1.18 (t, J = 7.3 Hz, 3H, CH_3CH$_2$), 1.45 (ddt, J = 4.8, 12.6, 4.8 Hz, 1H, H-7), 1.55 (ddd, J = 1.5, 4.8, 13.3 Hz, 1H, H-8), 159-1.73 (m, 2H, H-9), 1.82 (s, CH$_3$, 3H, H-8), 1.93 (d, J = 13.3 Hz, 1H, H-7), 2.67 (dt, J = 12.1, 3.0 Hz, 1H, H-6), 3.85 (s, 1H, H-5), 3.97-4.11 (m, 2H, CH$_3$CH_2), 4.39 (s, 1H, H-1); ^{13}C NMR (DMSO) δ 14.1, 17.9, 20.9, 27.8,

31.1, 45.5, 48.1, 59.7, 59.8, 69.2, 158.6, 172.6. Anal. Calcd for $C_{11}H_{17}NO_3$ (211.26): C, 62.54; H, 8.11; N, 6.63. Found: C, 63.00; H, 8.24; N, 6.32.

7b: Yield 65% from iodooxazine **6a**, and 62% from bromooxazine **6b**, a white crystalline solid, mp 64-65 °C; ^{1}H NMR (DMSO) δ 1.21 (t, J = 7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.38-1.52 (m, 1H, H-7), 1.63-1.74 (m, 2H, H-7, H-8), 1.82-1.89 (m, 1H, H-9), 1.93 (dt, J = 13.3, 1.8 Hz, 1H, H-9), 2.01-2.12 (m, 1H, H-8), 2.82 (dt, J = 12.1, 3.5 Hz, 1H, H-6), 4.10 (q, J = 7.0 Hz, 2H, CH$_3$C*H*$_2$), 4.17-4.20 (m, 1H, H-5), 4.68-4.72 (m, 1H, H-1), 7.39 (t, 7.5 Hz, 2H, *m*-Ph), 7.46 (t, J = 7.3 Hz, 1H, *p*-Ph), 7.81 (d, J = 7.3 Hz, 2H, *o*-Ph); ^{13}C NMR (DMSO) δ 14.5, 18.2, 28.1, 31.5, 46.1, 49.0, 60.1, 70.3, 127.1, 128.4, 130.8, 133.8, 156.8, 173.0. Anal. Calcd for $C_{16}H_{19}NO_3$ (273.34): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.39; H, 6.87; N, 5.43.

General synthesis of stereoisomeric 2-amino-4-hydroxy acids 8 and 11 and oxazinonecarboxylic acid 4: A solution of ester **3** or **7a,b** (1 mmol in 20 mL 20% HCl) was refluxed for 30 h. The solvent was then evaporated off to afford the crude amino acid hydrochloride. The free amino acid base was liberated by ion exchange chromatography with Dowex 50.

(*r*-6,*c*-1,*c*-5)-2-Oxa-3-oxo-4-azabicyclo[3.3.1]nonane-6-carboxylic acid (4): Yield 53% from **7a**, and 35% from **7b**, a white crystalline solid, mp 222-226 °C; ^{1}H NMR (DMSO) δ 1.52-1.67 (m, 2H, H-5, H-6), 1.69-1.80 (m, 1H, H-6), 1.82-1.98 (m, 3H, H-3, H-5), 2.51-2.59 (m, 1H, H-1), 3.79 (br s, 1H, H-2), 4.51 (br s, 1H, H-4), 7.28 (d, J = 5.04 Hz, 1H, O*H*); ^{13}C NMR (DMSO) δ 18.4, 29.1, 30.1, 46.0, 46.7, 72.1, 153.8, 174.3. Anal. Calcd for $C_8H_{11}NO_4$ (185.18): C, 51.89; H, 5.99; N, 7.56. Found: C, 5.92; H, 5.57; N, 7.92.

(*r*-1,*c*-2,*c*-4)-2-Amino-4-hydroxycyclohexanecarboxylic acid (8): Yield 52 %, a white crystalline solid, mp 220-225 °C; ^{1}H NMR (D_2O) δ 1.41 (1H, s, H-5), 1.55-1.67 (m, 1H, H-6), 1.78-1.91 (m, 2H, H-3, H-5), 2.06 (dt, J = 12.6, 3.5 Hz, 1H, H-3), 2.10-2.22 (m, 1H, H-6), 2.58 (q, J = 4.4 Hz, 1H, H-2), 3.49 (t, J = 13.6, 4.1 Hz, 1H, H-1), 3.88 (m, 1H, H-4); ^{13}C NMR (D_2O) δ 22.9, 30.8, 34.7, 42.6, 49.0, 67.5, 180.3. Anal. Calcd for $C_7H_{13}NO_3$ (159.19): C, 52.82; H, 8.23; N, 8.80. Found: C, 52.99; H, 8.48; N, 8.70.

(*r*-1,*t*-2,*t*-4)-2-Amino-4-hydroxycyclohexanecarboxylic acid (11): Yield 48%, a white crystalline solid, mp 230-232 °C; ^{1}H NMR (D_2O) δ 1.27-1.5 (m, 3H, H-3, H-5, H-6), 2.02-2.08 (m, 1H, H-5), 2.14-2.26 (m, 2H, H-2, H-6), 2.28-2.34 (m, 1H, H-3), 3.35 (ddd, J = 4.0, 10.8, 12.1 Hz, 1H, H-1), 3.76 (tt, J = 4.0, 10.8 Hz, 1H, H-4); ^{13}C NMR (D_2O) δ 25.7,

35.2, 41.0, 45.8, 50.5, 67.5, 180.5. Anal. Calcd for $C_7H_{13}NO_3$ (159.19): C, 52.82; H, 8.23; N, 8.80. Found: C, 52.54; H, 8.73; N, 8.49.

***cis*-2-Benzoylamino-4-cyclohexenecarboxylic acid (12a):** 2-Amino-4-cyclohexene-carboxylic acid (1.41 g, 10 mmol) was dissolved in 10% NaOH solution (15 mL), benzoyl chloride (1.54 g, 11 mmol) was added dropwise, and the solution was stirred at room temperature for 1 h. The solution was then acidified with aqueous HCl, and the precipitated **12a** was filtered off, washed with water and dried. Yield 2.05 g, 84%, a white crystalline solid, mp 188-189 °C (*n*-hexane–ethyl acetate); ^{1}H NMR (DMSO) δ 2.30 (m, 1H, H-2), 2.55 (m, 1H, H-2), 2.90 (dd, J = 6.0, 9.5 Hz, 1H, H-1), 4.41-4.48 (m, 1H, H-6), 5.68 (d, J = 10.3 Hz, 1H, H-3), 5.62(d, J = 10.3 Hz, 1H, H-4), 7.52 (t, J = 7.3 Hz, 1H, *p*-Ph), 7.45 (t, J = 7.3 Hz, 2H, *o*-Ph), 7.79 (d, J = 7.30 Hz, 2H, *m*-Ph), 7.97 (d, J = 8.2 Hz, 1H, NH), 12.28 (br s, 1H, OH); ^{13}C NMR (DMSO) δ 26.1, 30.2, 41.6, 46.1, 125.4, 126.1, 128.2, 129.0, 131.9, 135.6, 167.0, 175.3. Anal. Calcd for $C_{14}H_{15}NO_3$ (245.28): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.94; H, 7.43; N, 5.39.

***cis*-2-*tert*-Butoxycarbonylamino-4-cyclohexenecarboxylic acid (12b):** 2-Amino-4-cyclohexenecarboxylic acid (1.41 g, 10 mmol) was dissolved in a mixture of dioxane (20 mL) and water (10 mL), *tert*-butoxypyrocarbonate (2.4 g, 11 mmol) was added to the solution at 0 °C , and the mixture was stirred at room temperature for 4 h. The solvent was then evaporated to down half volume, and the mixture was diluted with ethyl acetate (20 mL) and next acidified with 10% H_2SO_4 (pH = 2.5). The mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layer was dried (Na_2SO_4) and evaporated. The residue was recrystallized from diisopropyl ether to give a white crystalline solid. ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s, OtBu), 2.21 (dd, J = 18.1 Hz, 6.04 Hz, 1H, H-2), 2.36 (d, J = 18.1 Hz, 2H, H-5), 2.54 (d, J = 18.1 Hz, 1H, H-2), 2.81-2.93 (m, 1H, H-1), 4.11-4.23 (m, 1H, H-6), 5.29 (d, J = 6.04 Hz, 1H, NH), 5.55-5.70 (m, H-3, 2H, H-4); ^{13}C NMR (DMSO) δ 26.8, 28.9, 31.8, 42.6, 46.8, 80.1, 125.3, 125.7, 156.1, 179.1.Yield 75 %, mp 58-60 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H, OtBu), 2.21 (dd, J = 18.1 Hz, 6.04 Hz, 1H, H-2), 2.36 (d, J = 18.1 Hz, 2H, H-5), 2.54 (d, J = 18.1 Hz, 1H, H-2), 2.81-2.93 (m, 1H, H-1), 4.11-4.23 (m, 1H, H-6), 5.29 (d, J = 6.04 Hz, 1H, NH), 5.55-5.70 (m, 2H, H-3, H-4); ^{13}C NMR (DMSO) δ 26.8, 28.9, 31.8, 42.6, 46.8, 80.1, 125.3, 125.7, 156.1, 179.1. Anal. Calcd for $C_{12}H_{19}NO_4$ (241.29): C, 59.73; H, 7.94; N, 5.80. Found: C, 59.42; H, 7.81; N, 5.92.

***trans*-6-*tert*-Butoxycarbonylaminocyclohex-3-ene-carboxylic acid (16):** The procedure described for **12b** was followed to prepare **16** from *trans*-6-aminocyclohex-3-ene-carboxylic

acid. Yield 74%, a white crystalline solid, mp 120-122 °C; ^{1}H NMR (DMSO) δ 1.36 (s, 9H, OtBu), 1.88-1.97 (m, 1H, H-2), 2.15-2.23 (m, 3H, H-2, H-5), 2.44-2.54 (m, 1H, H-6), 3.6-3.72 (m, 1H, H-1), 5.55-5.63 (m, 2H, H-3, H-4), 6.76 (d, J = 8.6 Hz, 1H, NH); ^{13}C NMR (DMSO) δ 28.3, 28.6, 31.5, 44.6, 47.5, 77.8, 126.1, 125.3, 155.2, 175.5. Anal. Calcd for $C_{12}H_{19}NO_4$ (241.29): C, 59.73; H, 7.94; N, 5.80. Found: C, 59.39; H, 7.49; N, 5.53.

General procedure for the synthesis of iodolactones 13a,b and 17: To a solution of carboxylic acid derivative **12a,b** or **16** (5.75 mmol) in CH_2Cl_2 (50 mL), 0.5 N $NaHCO_3$ solution (35 mL), KI (5.7 g, 34.5 mmol) and I_2 (2.9 g, 11.5 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 20 h and then poured into 100 mL saturated $Na_2S_2O_3$ solution. The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated. The residue was recrystallized from diisopropyl ether to give iodolactones **13a,b** and **17**.

13a: Yield 78%, a white crystalline solid, mp 185-189 °C; ^{1}H NMR (DMSO) δ 2.22 (dd, J = 5.3, 15.8 Hz, 1H, H-3), 2.51-2.80 (m, 3H, H-8, H-3), 2.81 (d, J = 12.4 Hz, 1H, H-1), 4.23-4.31 (1H, m, H-2), 4.75 (t, J = 4.8 Hz, 1H, H-4), 4.89 (t, J = 4.8 Hz, 1H, H-5), 7.48 (t, J = 7.3 Hz, 2H, *m*-Ph), 7.55 (t, J = 7.3 Hz, 1H, *p*-Ph), 7.83-7.87 (d, J = 7.3 Hz, 2H, *o*-Ph), 8.53 (d, J = 7.0 Hz, 1H, NH); ^{13}C NMR (DMSO) δ 23.4, 33.4, 34.6, 43.9, 46.0, 79.3, 127.8, 128.6, 131.8, 134.3, 166.9, 175.9. Anal. Calcd for $C_{14}H_{14}INO_3$ (371.18): C, 45.30; H, 3.80; N, 3.77. Found: C, 44.92, H, 3.61; N, 3.87.

13b: Yield 84%, a white crystalline solid, mp 170-174 °C; ^{1}H NMR (DMSO) δ 1.40 (s, 9H, OtBu), 2.09 (dd, J = 5.8, 16.1 Hz, 1H, H-3), 2.27 (ddd, J = 5.8, 12.3, 16.1, 1H, H-3), 2.46 (ddd, J = 1.5, 5.8, 12.6 Hz, 1H, H-8), 2.55 (d, J = 12.6 Hz, 1H, H-8), 2.67 (d, J = 6.3 Hz, 1H, H-1), 3.69-3.79 (m, 1H, H-2), 4.66 (t, J = 5.3 Hz, 1H, H-4), 4.82 (dd, J = 4.3, 5.3 Hz, 1H, H-5), 7.17 (d, J = 7.3 Hz, 1H, N*H*CO); ^{13}C NMR (DMSO) δ 23.2, 28.5, 33.2, 34.9, 44.2, 46.7, 78.8, 79.1, 155.2, 175.8. Anal. Calcd for $C_{12}H_{18}INO_4$ (367.19): C, 39.25; H, 4.94; N, 3.81. Found: C, 38.93; H, 4.65; N, 3.72.

17: Yield 82%, a white crystalline solid, mp 125-127 °C; ^{1}H NMR (DMSO) δ 1.41 (s, 9H, OtBu), 2.25-2.38 (m, 2H, H-3, H-8), 2.41-2.48 (m, 1H, H-3), 2.75 (t, J = 4.1 Hz, 1H, H-8), 2.88 (d, J = 12.8 Hz, 1H, H-1), 3.75 (s, 1H, H-5), 4.42 (s, 1H, H-4), 4.94 (dd, J = 3.3, 5.8 Hz, 1H, H-2), 6.93 (br s, 1H, N*H*); ^{13}C NMR (DMSO) δ 19.5, 28.0, 28.6, 33.3, 42.4, 46.0, 78.8,

81.2, 176.5. Anal. Calcd for $C_{12}H_{18}INO_4$ (367.19): C, 39.25; H, 4.94; N, 3.81. Found: C, 39.37; H, 5.22; N, 3.68.

Reduction of iodolactones 13a,b and 17 to lactones 14a,b and 18: Tributyltin hydride (2.4 mL, 9 mmol) was added to a solution of iodolactone **13a,b** or **17** (4.5 mmol) in dry CH_2Cl_2 (65 mL) under an argon atmosphere. After stirring for 20 h at 40 °C, the solvent was evaporated off and the crude lactone was crystallized from *n*-hexane, and recrystallized from isopropyl ether–ethyl acetate.

14a: Yield 68%, a white crystalline solid, mp 188-190 °C; ^{1}H NMR (DMSO) δ 1.79-2.12 (m, 5H, H-3, H-4, H-8), 2.50-2.57 (m, 1H, H-8), 2.88 (d, J = 5.8 Hz, 1H, H-1), 4.20-4.29 (m, 1H, H-5), 4.94 (t, J = 4.8 Hz, 1H, H-2), 7.60 (t, J = 7.3 Hz, 2H, *m*-Ph), 7.67 (t, J = 7.3 Hz, 1H, *p*-Ph), 7.98 (d, J = 7.3 Hz, 2H, *o*-Ph), 8.50 (d, J = 7.0 Hz, 1H, N*H*); ^{13}C NMR (DMSO) δ 23.9, 27.4, 35.6, 43.6, 48.3, 77.0, 127.8, 128.5, 131.7, 134.5, 166.8, 176.9. Anal. Calcd for $C_{14}H_{15}NO_3$ (245.28): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.49; H, 6.33; N, 5.49.

14b: Yield 75%, a white crystalline solid, mp 115-119 °C; ^{1}H NMR (DMSO) δ 1.40 (s, 9H, O*tBu*), 1.45-1.56 (m, 1H, H-3), 1.57-1.65 (m, 1H, H-3), 1.75-1.9 (m, 3H, H-4, H-8), 2.29-2.37 (m, 1H, H-8), 2.62 (d, J = 4.8 Hz, 1H, H-1), 3.56-3.65 (m, 1H, H-5), 4.73 (t, J = 4.8 Hz, 1H, H-2), 6.95 (d, J = 6.5 Hz, 1H, N*H*); ^{13}C NMR (DMSO) δ 24.3, 27.4, 28.5, 35.5, 43.8, 49.1, 76.7, 78.3, 155.1, 176.7. Anal. Calcd for $C_{12}H_{19}NO_4$ (241.29): C, 59.73; H, 7.94; N, 5.80. Found: C, 59.92; H, 8.21; N, 5.37.

18: Yield 72%, a white crystalline solid, mp 82-86 °C; ^{1}H NMR (DMSO) δ 1.40 (s, 9H, OtBu), 1.53-1.61 (dd, J = 6.3, 14.6 Hz, 1H, H-8), 1.66-1.85 (m, 2H, H-3, H-4), 2.05-2.18 (m, 2H, H-4, H-8), 2.69 (t, J = 4.3 Hz, 1H, H-1), 3.69-3.78 (m, 1H, H-5), 4.81 (t, J = 4.3 Hz, 1H, H-3), 7.48 (1H, br s, N*H*); ^{13}C NMR (DMSO) δ 24.0, 24.8, 28.6, 31.0, 43.1, 45.6, 78.1, 78.56, 177.3. Anal. Calcd for $C_{12}H_{19}NO_4$ (241.29): C, 59.73; H, 7.94; N, 5.80. Found: C, 59.56; H, 7.83; N, 5.52.

General procedure for 2-amino-5-hydroxycarboxylic acids 15 and 19 from lactones 14b and 18: Lactone **14b** or **18** (0.72 g, 3 mmol) was dissolved in 20 mL of 20% aqueous HCl and the solution was stirred at room temperature for 10 h. The solvent was next evaporated off, and the amino acid base was liberated from the residual hydrochloride by ion-exchange chromatography on Dowex 50.

(*r*-1,*c*-2,*c*-5)-2-Amino-5-hydroxycyclohexanecarboxylic acid (15): Yield 66%, a white crystalline solid, mp, 255-256 °C; ^{1}H NMR (D_2O) δ 1.43-1.54 (m, 1H, H-4), 1.61 (q, J = 11.8 Hz, 2H, H-6), 1.78 (tt, J = 4.3, 13.6 Hz, 1H, H-3), 1.85-1.93 (m, 1H, H-4), 2.02 (ddt, J = 4.3, 14.9, 4.3 Hz, 1H, H-3), 2.15 (d, J = 13.6 Hz, 1H, H-6), 2.62 (dt, J = 12.1, 3.8 Hz, 1H, H-1), 3.64 (q, J = 3.8 Hz, 1H, H-2), 3.75-3.84 (m, 1H, H-5); ^{13}C NMR (D_2O) δ 25.5, 27.9, 32.4, 43.7, 47.9, 68.2, 180.5. Anal. Calcd for $C_7H_{13}NO_3$ (159.19): C, 52.82; H, 8.23; N, 8.80. Found: C, 52.67; H, 8.49; N, 8.31.

(*r*-1,t-2,*c*-5)-2-Amino-5-hydroxycyclohexanecarboxylic acid (19): Yield 62%, a white crystalline solid, mp 275-280 °C; ^{1}H NMR (D_2O) δ 1.32-1.44 (m, 2H, H-4, H-6), 1.53 (ddt, J = 3.5, 12.8, 3.5 Hz, 1H, H-3), 2.01-2.14 (m, 2H, H-3, H-4), 2.31-2.40 (m, 2H, H-1, H-6), 3.24 (dt, J = 3.8, 11.3 Hz, 1H, H-2), 3.73 (tt, J = 4.0, 11.1 Hz, 1H, H-5); ^{13}C NMR (D_2O) δ 27.7, 32.0, 36.9, 46.8, 51.5, 68.8, 179.8. Anal. Calcd for $C_7H_{13}NO_3$ (159.19): C, 52.82; H, 8.23; N, 8.80. Found: C, 52.55; H, 8.43; N, 8.21.

(1*S*,2*R*,4*R*)-2-Amino-4-hydroxycyclohexanecarboxylic acid (+)-(8): The synthesis was carried out similarly as for the racemic compound (±)-**8**, starting from (1*S*,2*R*)-2-amino-4-cyclohexenecarboxylic acid hydrochloride, via intermediate **5a**. The ^{1}H NMR data on the intermediates and products were similar to those for the racemates. Representative data on the enantiomers isolated:

(1*S*,2*R*)-Ethyl 2-amino-4-cyclohexenecarboxylate: Colourless crystals, mp 125-128 °C, $[\alpha]_D^{20}$ +19 (c 1.0, EtOH), ee > 99%.

(+)-1a. . A colourless oil, $[\alpha]_D^{20}$ +58 (c 0.6, MeOH), ee > 99%.

(+)-7a. . A colourless oil, $[\alpha]_D^{20}$ +28 (c 0.4, MeOH).

(+)-(8). Colourless crystals, mp 140-145 °C, $[\alpha]_D^{20}$ +17 (c 0.23, H_2O), ee > 99%.

(1*S*,2*R*,5*R*)-2-Amino-5-hydroxycyclohexanecarboxylic acid (-)-(15): The synthesis was carried out similarly as for the racemic compound (±)-**15**, starting from (1*S*,2*R*)-2-amino-4-cyclohexenecarboxylic acid hydrochloride, via intermediate **13b**. The ^{1}H NMR data on the intermediates and products were similar to those for the racemates. Representative data on the enantiomers isolated:

(+)-(12b). Colourless crystals, mp 118-123 °C, $[\alpha]_D^{20}$ +19.4 (c 0.5, MeOH), ee > 99%.

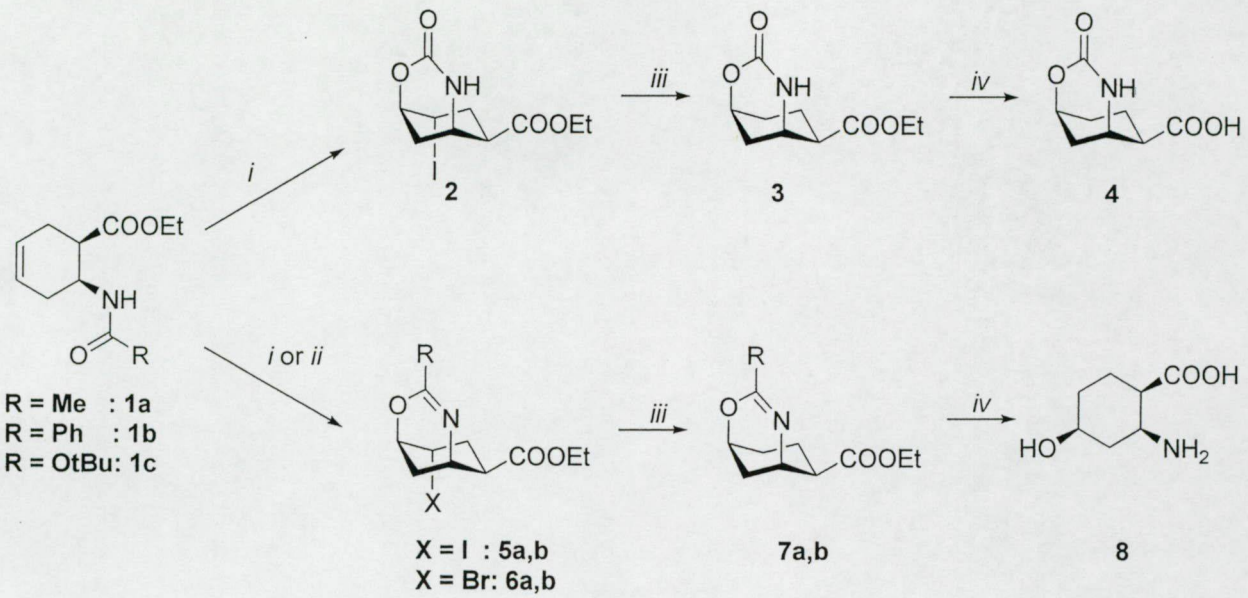
(+)-(13b). Colourless crystals, mp 185-190 °C, $[\alpha]_D^{20}$ +92.5 (c 0.6, MeOH).

(+)-(14b). Colourless crystals, mp 135-140 °C, $[\alpha]_D^{20}$ +104 (c 0.1, MeOH), ee > 99%.

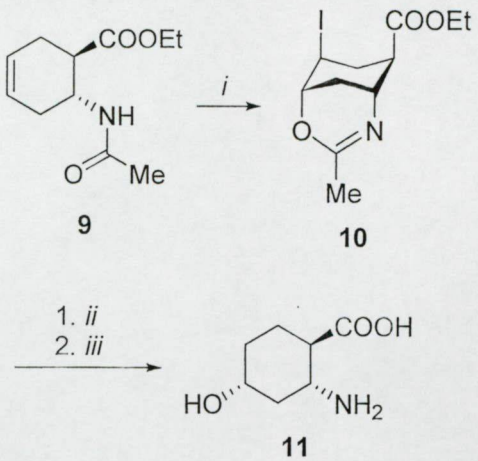
(-)-(15). Colourless crystals, mp 247-250 °C, $[\alpha]_D^{20}$ -26 (c 0.15, H_2O), ee > 99%.

X-ray data collection and processing: Crystallographic data for **15** were collected at 173 K on a Nonius Kappa CCD area-detector diffractometer, using graphite monochromatized MoK_α radiation (λ = 0.71073 Å). The data collection was performed using φ and ω scans. The data were processed using DENZO-SMN v0.93.0.[15] The structures were solved by direct methods with the *SHELXS* program[16] and full-matrix least-squares refinements on F^2 were performed, using the *SHELXL-97* program [16]. All heavy atoms were refined anisotropically. The OH and NH hydrogens were refined anisotropically. The CH hydrogen atoms were included at fixed distances with fixed displacement parameters from their host atoms. Figure 1 was drawn with *Ortep-3 for Windows* [17].

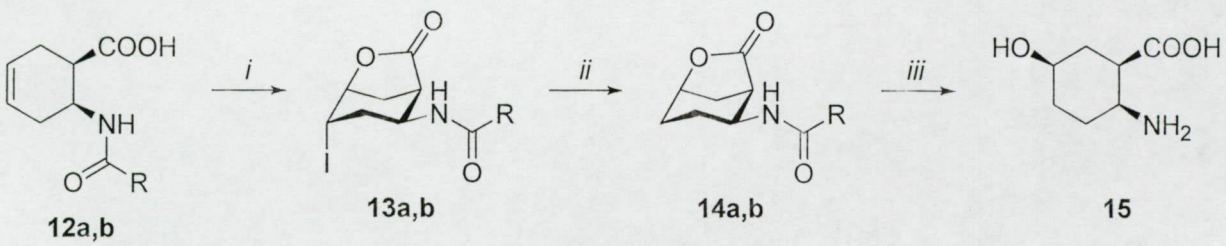
Acknowledgment. We thank the Hungarian Research Foundation (OTKA No. T 049407 and TS 04888) for financial support.



Scheme 1. (*i*) NIS, CH_2Cl_2, 14 h, rt; (*ii*) NBS, CH_2Cl_2, 14 h, rt; (*iii*) Bu_3SnH, CH_2Cl_2, 20 h, 40 °C; (*iv*) 20% HCl, 30 h reflux.

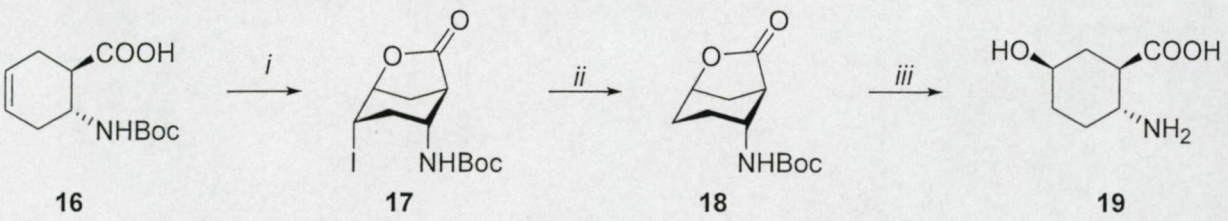


Scheme 2. (*i*) NIS, CH_2Cl_2, 14 h, rt; (*ii*) Bu_3SnH, CH_2Cl_2, 20 h, 40 °C; (*iii*) 20% HCl, 30 h reflux.



R = Ph: **a**; R = OBu^t: **b**

Scheme 3. (*i*) KI, I_2, $NaHCO_3$, CH_2Cl_2, 20 h, rt; (*ii*) Bu_3SnH, CH_2Cl_2, 20 h, 40 °C; (*iii*) 20% HCl, 30 h rt.



16 **17** **18** **19**

Scheme 4. (*i*) KI, I_2, $NaHCO_3$, CH_2Cl_2, 20 h, rt; (*ii*) Bu_3SnH, CH_2Cl_2, 20 h, 40 °C; (*iii*) 20% HCl, 30 h, rt.

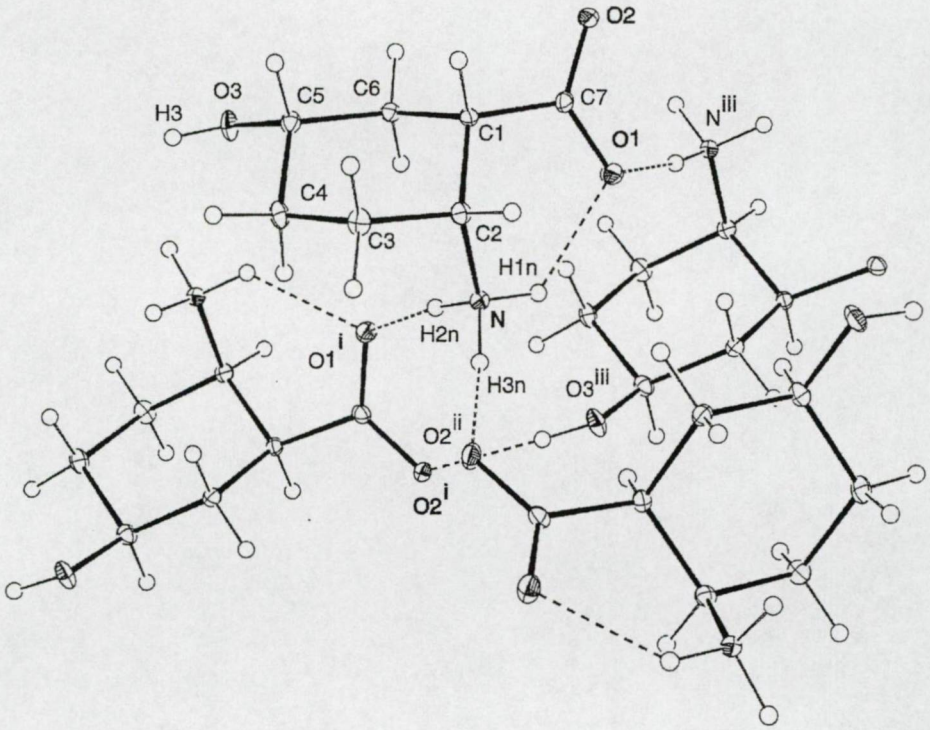
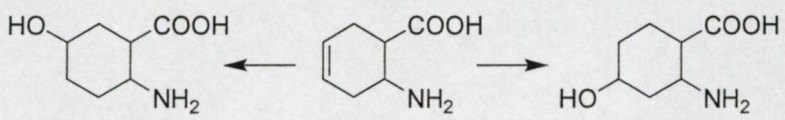


Figure 1. Crystal structure of **15,** showing the hydrogen bonding scheme. Thermal ellipsoids have been drawn at the 30% probability level. Symmetry codes: i = x+1/2,-y+3/2,-z+2, ii = -x+3/2,-y+1,z+1/2 and iii = x+1/2,-y+3/2,-z+1.

Graphical Abstract



cis, trans

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VII.

Synthesis and stereostructure of 3-amino-5- and -6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid diastereomers

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Summary. *All-endo*-3-amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid (**4**) and two epimers of 3-amino-6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid (**9, 10**) were prepared via 1,3-oxazine or γ-lactone intermediates by the stereoselective functionalization of *endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid derivatives (**1, 5**). Their structures were proved by IR and NMR spectroscopy, with the use of HMQC, HMBC, DEPT and DIFFNOE techniques.

Keywords. Amino acids; Heterocycles; IR spectroscopy; NMR spectroscopy; Cyclization.

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Introduction

During the past decade considerable attention has been directed towards the synthesis of hydroxy-β-amino acids [1-6]. These compounds constitute an important class of amino acids, because of their occurrence in many biologically relevant compounds, including Paclitaxel (Taxol) and Docetaxel (Taxotere), which are among the most effective chemotherapeutic agents [7, 8]. The alicyclic hydroxy-β-amino acids can be used as building blocks for the preparation of modified analogues of biologically active peptides [9, 10]. Hydroxylated alicyclic β-amino acids and their derivatives can be widely used for the synthesis of various heterocyclic compounds [11-17]. Our present aim was the synthesis and structure analysis of the title hydroxylated alicyclic β-amino acids.

Results and Discussion

The key step in the synthesis of *all-endo*-3-amino-6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid (**4**) the stereoselective iodolactonization [15] of *N*-Boc-*endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid derivative (**1**). The iodolactonization was performed under two-phase conditions, furnishing iodolactone **2**, which was reduced with Bu_3SnH to give lactone **3**. The *N*-Boc lactone was converted to the *all-endo* isomer of hydroxy-amino acid **4** by acidic hydrolysis (Scheme 1).

< Scheme 1 >

When *N*-acetylamino ester **5** was reacted with *N*-iodosuccinimide [16] (NIS) or *N*-bromosuccinimide (NBS) a tricyclic 1,3-iodo- or -bromooxazine derivative (**6a,b**) was obtained stereoselectively. When dehalogenated with Bu_3SnH under an argon atmosphere, **6a,b** yielded **7**. The hydrolysis of oxazine **7** with dilute hydrochloric acid at room temperature gave *N*-acetyl-hydroxy amino acid **8**. When **8** was boiled in acidic solution, *endo* → *exo* isomerization took place and the forced conditions resulted in 3,5-*diendo*-2-*exo*-3-amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride (**9**) as the main product. The mother liquor was treated with a large excess of propylene oxide and, after fractional crystallisation, compound **10** was isolated as a diastereomerically enriched (8:2) mixture (Scheme 2). The correct configurations of hydroxylated amino acids **9** and **10** were proved indirectly, the stereostructures of **8** and **11** being demonstrated with a using DIFFNOE technique and also by chemical transformation: esterification of **9** led to hydroxylated amino ester **11**, while after acetic acid treatment **10** gave an *N*-acetyl derivative. The NMR spectrum of the resulted compound was identical with that of *all-endo*-3-acetylamino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid **8**.

< Scheme 2 >

The constitutions and stereostructure of the new compounds **2-5** and **7-11** were determined by IR, ^1H and ^{13}C NMR spectroscopy (Tables 1 and 2). The spectral data are self-explanatory; only a few additional remarks are necessary. It should be noted that, for easier comparison of analogous spectral data, the numbering of **1** given in Scheme 1 will be used for all compounds in this section and also in Tables 1 and 2.

< Table 1 >

< Table 2 >

1) The *diendo* arrangement of the 2,3 substituents in compounds **2-5**, **7** and **8** follows from our "splitting rule" [17, 18] In consequence of the dihedral angles of *ca.* 90°, the 1,2- and 3,4- vicinal H,H-couplings do not cause double spliting of the H–2 and H–3 signals in the *diexo* compounds, whereas these couplings lead to a well-detectable split by 2-4 Hz in the case of the *diendo* anellated molecules, where the dihedral angles are *ca.* 30°. Hence, as a consequence of the H–2,H–3 interaction, H–2 and H-3 exhibit doublets in the *diexo* derivatives and double doublet signals in the *diendo* analogues. The H–2,3 coupling results in a 7-11 Hz split due to the dihedral angle of 0° for the *diendo* and *diexo* anellated compounds [17], while this coupling constant is expected to be smaller (*ca.* 4-6 Hz) for *exo-endo* derivatives [19], where the dihedral angle is *ca.* 109°. Thus, the *dd* (**2-4**), *dt* (**5**), *ddd* (**7**) or *td* (**8**) split of the H-2 (**2-5**) or H-3 (**7**, **8**) signal confirms the 2,3-*diendo* configuration. Higher than *dd* splits are due to couplings with the NH (**5**) or H-7(*exo*) (**7**, **8**).

The similar ^{13}C NMR chemical shifts in **3** and **4** demonstrate the unaltered *all-endo* orientation of the three substituents in **4** as compared with **3**.

In the ^{1}H NMR spectrum of **9**, the H-2 and H-3 signals are *d*'s, split by 4.3 Hz, and consequently this molecule must have the *endo-exo* configuration. In accordance, the C–1 and C–4 chemical shifts in **9** are dramatically higher (by 8.0 and 8.6 ppm) because of the absence of a field effect [20] causing opposite shifts to those in **8**, due to very strong hindrance between the three *endo* substituents. Hence, during the acidic hydrolysis of **8**, *endo* → *exo* isomerisation occurred, probably in position **2**, *via* the enolic form of the carboxyl group.

The practically identical ^{13}C NMR chemical shifts of **9** and **11** confirm analogous stereostructures for these molecules. For **11**, DIFFNOE measurements unambiguously proved the 2-*exo*-3-*endo* configuration. On saturation of the H-2 doublet (at 2.59 ppm), for example the H-6(*exo*) signal (at 1.24 ppm) responded, while for the H-7(*endo*) signal an intensity enhancement

was not observed. The DIFFNOE measurements together with the HMQC and HMBC spectra also furnished proof of the assignments.

2) In the ^{13}C NMR spectrum of **2** the very characteristic upfield-shifted line of iodo-substituted carbon (C–5) [21] appears at 24.5 ppm. The β-effect of the iodo substituent [22] is revealed in a downfield shift by 7.5 and 8.5 ppm of the C–4 and C–6 lines as compared with **3**. An anisotropic neighbouring deshielding effect of the iodine atom is also observable on the H–7 signals in the ^{1}H NMR spectrum, which are downfield-shifted in **2** (by 0.36 and 0.61 ppm) as compared with **3**. This supports the *ab ovo* more probable *exo* position of the iodine atom [to avoid the steric interaction between 2(*endo*)-I and O-4(*endo*)].

3) The ^{1}H NMR signal (a singlet of 9H intensity) of the methyl group and its carbon line in ^{13}C NMR spectrum, together with the line of the quaternary carbon atom, are proof of the presence of the *t*-Bu group in **2** and **3**.

4) The position of the hydroxy group in **4** follows from the structures of **2** and **3** containing a γ-lactone ring, the presence of which is proven by the high IR carbonyl frequency [23] (1788 and 1775 cm^{-1} in **2** and **3**, respectively).

5) In the spectra of **5, 7** and **11**, all the IR, ^{1}H and ^{13}C NMR signals of the COOEt group appear and the rigid structure of **7** results in a series of long-range couplings, which lead to higher multiplicities of all signals observed in this case only in the ^{1}H NMR spectrum.

6) The downfield shift of the methyl (Ac) signal (by 0.49 ppm) in the ^{1}H NMR spectrum of **8** relative to **5** is noteworthy; this is caused by the anisotropic effect [24] of the *endo*-OH group.

Experimental

General Procedures. Melting points were determined on a Kofler micro melting point apparatus and are uncorrected. Elemental analyses were conducted with a Perkin-Elmer CHNS-2400 Ser II Elemental Analyser; the results were found to be in good agreement (±0.2%) with the calculated values. Merck Kieselgel $60F_{254}$ plates were used for TLC: the eluent was toluene:MeOH 4:1. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500.13 (^{1}H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. DEPT spectra were run in a standard manner, using only the $\Theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The HMQC and HMBC spectra were obtained by using the standard Bruker pulse programs.

(1*S**,2*R**,3*S**,4*R**)-3-*tert*-Butoxycarbonylaminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**1**, $C_{12}H_{17}NO_4$) [25]

1 M NaOH (20 cm^3) was added to a solution of 3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid [26] (3.1 g, 20 mmol) in 60 cm^3 of a 2:1 dioxane:H_2O mixture. The solution was cooled to 0 °C in an ice bath and di-*tert*-butyl dicarbonate (Boc_2O) was added slowly. The mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for 4 h. The solvent was concentrated to 20 cm^3 on a rotatory evaporator, the pH was then adjusted to 2.5 with 10% H_2SO_4, and the resulting solution was extracted with EtOAc (3x50 cm^3). The combined extracts were dried (Na_2SO_4), and evaporated, to give **1** as a white solid, which was recrystallized from iPr_2O: m.p. 183-187 °C; yield 3.59 g (75%); lit. m.p. 126-127 °C [27].

(1*S**,2*S**,3*S**,6*R**,7*R**,9*S**)-9-*tert*-Butoxycarbonylamino-2-iodo-4-oxatricyclo[4.2.1.$0^{3,7}$]nonan-5-one (**2**, $C_{13}H_{18}INO_4$)

To a solution of *N*-Boc-carboxylic acid **1** (2.75 g, 11.5 mmol) in CH_2Cl_2 (100 cm^3), $NaHCO_3$ solution (0.5 N, 70 cm^3), KI (11.62 g, 70 mmol) and I_2 (5.84 g, 23 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 20 h and then poured into 10% aqueous $Na_2S_2O_3$ solution (50 cm^3). The reaction mixture was extracted with CH_2Cl_2 (3 x 20 cm^3) and the combined extract was washed with brine (20 cm^3), dried (Na_2SO_4), and evaporated. The residue was recrystallized from iPr_2O, m.p. 183-187 °C; yield 3.66 g (84%).

(1*R**,3*R**,6*R**,7*R**,9*S**)-9-*tert*-Butoxycarbonylamino-4-oxatricyclo[4.2.1.$0^{3,7}$]nonan-5-one (**3**, $C_{13}H_{19}NO_4$)

Bu_3SnH (4.8 cm^3, 18 mmol) was added to a solution of iodolactone **2** (4.41 g, 9 mmol) in dry CH_2Cl_2 (65 cm^3) under an argon atmosphere. After stirring for 20 h, at 40 °C, the solvent was evaporated off and the lactone residue **3** was crystallized from *n*-hexane, and recrystallized from iPr_2O-EtOAc, m.p. 145-150 °C; yield 1.26 g (55%).

(1*R**,2*R**,3*S**,4*R**,6*R**)-3-Amino-6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride (**4**, $C_8H_{14}ClNO_3$)

Compound **3** (1.01 g, 4 mmol) was dissolved in aqueous HCl (20%, 20 cm^3) and the solution was stirred at room temperature for 10 h. The solvent was next evaporated off and the residue was recrystallized from H_2O-acetone, m.p. 220-222 °C, yield 0.70 g (84%).

Ethyl (1*S**,2*R**,3*S**,4*R**)-3-acetylaminobicyclo[2.2.1]hept-5-ene-2-carboxylate (**5**, $C_{12}H_{17}NO_3$)

To a suspension of ethyl 3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate hydrochloride [28] (2.17 g, 10 mmol) in toluene (40 cm^3), triethylamine (2.04 g, 20 mmol), and acetyl chloride (0.94 g, 12 mmol) were added and the reaction mixture was stirred at room temperature for 2 h, and then washed with H_2O (2 x 10 cm^3). The aqueous layer was extracted with EtOAc (3 x 20 cm^3). The combined organic layer was dried (Na_2SO_4) and evaporated. The residue was recrystallized from *n*-hexane-*i*Pr_2O, m.p. 64-67 °C; yield 1.67 g (75%).

Ethyl (1*R**,2*R**,3*R**,7*S**,8*R**,10*R**)-2-iodo-5-methyl-4-oxa-6-azatricyclo[5.2.1.$0^{3,8}$]dec-5-ene-10-carboxylate (**6a**, $C_{12}H_{16}INO_3$) and
Ethyl (1*R**,2*R**,3*R**,7*S**,8*R**,10*R**)-2-bromo-5-methyl-4-oxa-6-azatricyclo[5.2.1.$0^{3,8}$]-dec-5-ene-10-carboxylate (**6b**, $C_{12}H_{16}BrNO_3$)
A solution of **5** (1.67 g, 7.5 mmol) in CH_2Cl_2 (80 cm^3) was treated with *N*-iodosuccinimide (1.68 g, 7.5 mmol) or N-bromosuccinimide (1.34 g, 7.5 mmol) and subsequently stirred for 14 h at room temperature. When the reaction was completed, the mixture was washed with 10% NaOH solution (3 x 10 cm^3). The aqueous solution was extracted with CH_2Cl_2 (3 x 40 cm^3), and the organic phase was dried (Na_2SO_4) and evaporated. The oily products (**6a**: 1.92 g (73%); **6b**: 2.07 g (91%), respectively) were sensitive to the air; they were therefore used without purification in the next step.

Ethyl (1*S**,3*S**,7*S**,8*S**,10*R**)-5-methyl-4-oxa-6-azatricyclo[5.2.1.0*3,8*]dec-5-ene-10-carboxylate (**7**, $C_{12}H_{17}NO_3$)
Bu_3SnH (2.9 cm^3, 11 mmol) was added to a solution of iodo- or bromooxazine **6a** or **6b** (5.5 mmol) in dry CH_2Cl_2 (65 cm^3) under an argon atmosphere. After stirring for 20 h at 40 °C, the solvent was evaporated off and the residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc 10:1) to afford 1,3-oxazine **7** as an oil (0.82 g (67%) from **6a**; and 0.84 g (69%) from **6b**).

(1S*,2*R**,3*S**,4*S**,5*R**)-3-Acetylamino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid (**8**, $C_{10}H_{15}NO_4$)

A solution of **7** (0.67 g, 3 mmol) in 20% aqueous HCl was stirred for 2 h. The solvent was then evaporated off to afford crude **8**, which was recrystallized from H_2O:acetone, m.p. 225-235 °C (with decomposition); yield 0.51 g (80%).

(1*S**,2*S**,3*S**,4*S**,5*R**)-3-Amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride (**9**, $C_8H_{14}ClNO_3$)

A solution of **8** (0.4 g, 1.8 mmol) in 20% aqueous HCl was refluxed for 30 h. The solvent was then evaporated off to afford crude **9**, which was recrystallized from EtOH-Et_2O, m.p. 240-245 °C (with decomposition); yield 0.21 g (55%).

(1*S**,2*R**,3*S**,4*S**,5*R**)-3-Amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid (**10**, $C_8H_{13}NO_3$)

The mother liquor of **9** was evaporated off and the residue was dissolved in absolute EtOH. To this solution, 10 equivalents of propylene oxide was added. After stirring and refluxing for 2 h the mixture was evaporated to afford a mixture of **10:9** = 8:2 as solid crystals, m.p. 230-235 °C (with decomposition); yield 0.1 g (32%).

Ethyl (1S*,2R*,3S*,4S*,5R*)-3-amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylate hydrochloride (**11**, $C_{10}H_{18}ClNO_3$)

Thionyl chloride (0.5 cm^3, 7 mmol) was added dropwise with stirring to 5 cm^3 of dry EtOH at -15 °C. (1*S**,2*S**,3*S**,4*S**,5*R**)-3-Amino-5-hydroxybicyclo-[2.2.1]heptane-2-carboxylic acid hydrochloride (**9**) (0.21 g, 1 mmol) was added in one portion to the mixture, which was then stirred for 30 min at 0 °C. After standing for 3 h at room temperature, the mixture was refluxed for a further 1 h

and next evaporated. The residue was recrystallized from EtOH-Et_2O, m.p. 210-211 °C, yield 0.22 g (93%).

Acknowledgements

The authors thank the Hungarian Research Foundation (OTKA grants T-043634, TS-040888, TS-040732 and TS-44742) for financial support.

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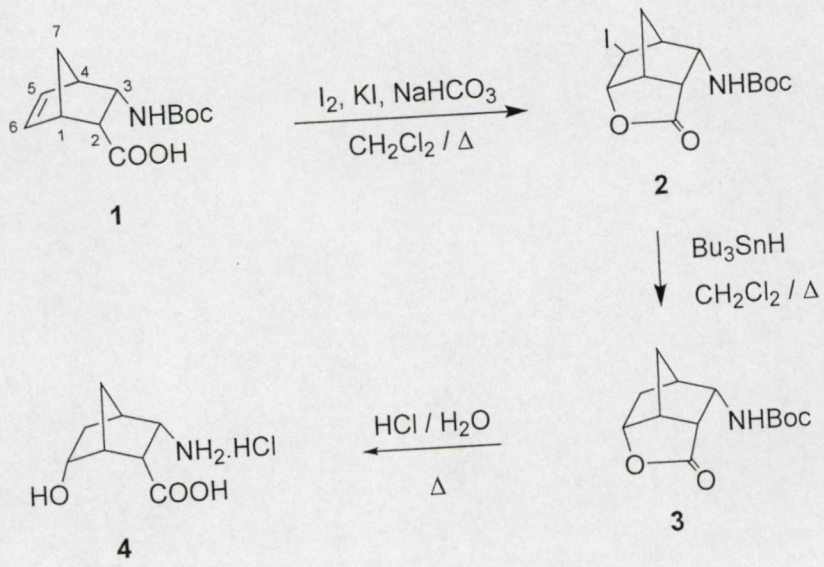
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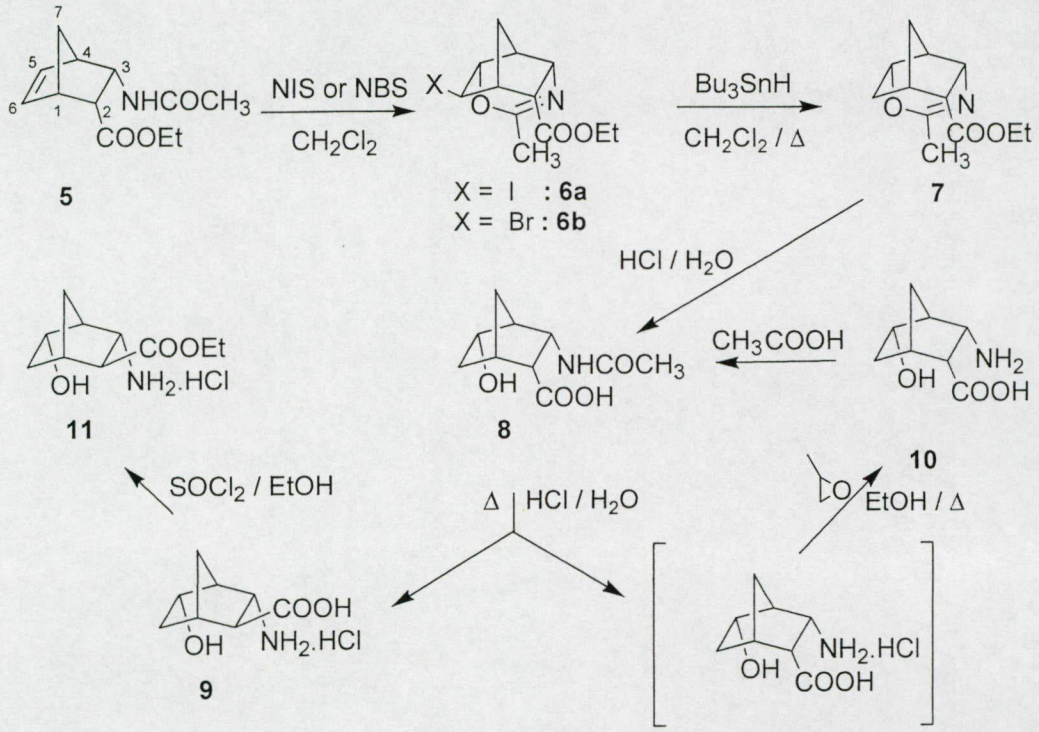
4
5
3
6
1
2
NHBoc
COOH
1
I2, KI, NaHCO3
CH2Cl2 / Δ
I
NHBoc
O
O
2
Bu3SnH
CH2Cl2 / Δ
NH2.HCl
HO
COOH
4
HCl / H2O
Δ
NHBoc
O
O
3

Scheme 1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COOEt
5
NIS or NBS
CH2Cl2
X = I : 6a
X = Br : 6b
Bu3SnH
CH2Cl2 / Δ
7
HCl / H2O
CH3COOH
NHCOCH3
COOH
8
NH2
COOH
10
EtOH / Δ
SOCl2 / EtOH
COOEt
NH2.HCl
11
Δ HCl / H2O
COOH
NH2.HCl
9
NH2.HCl
COOH

Scheme 2

Table 1. Characteristic IR frequencies[a] and ^{1}H NMR data[b] for compounds 2–5, 7–9 and 11[c]

Com-pound	Amide-I band[d]	νC=O band[e]	CH_3 s(9H)[f]	CH_3 *t*(3H)[g]	CH_2 *qa* (2H)[g]	NH broad[h]	H–1[i]	H–2[k]	H–3'[l]	H–4'[m]	H–5[n]	H–6[o]	CH_2(7)[p]
							norbornane/ene moiety						
2	1688	1788	1.44	–	–	4.15[r]	3.24	2.80	4.15[r]	2.90	~ 4.9	5.17	1.94, 2.34
3	1693	1775	1.42	–	–	4.81[r]	3.24	2.78	4.11	2.56	~ 1.75	4.81[r]	1.58, 1.73
4	–	1763	–	–	–	4.67	3.40	2.95	3.82	2.63	1.82, 1.90	5.01	1.70, 1.77
5	1654	1730	1.86	1.20	4.04	6.4	3.10[r]	3.13	4.72	3.10[r]	6.14	6.27	1.35, 1.45
7	1676	1733	1.86	1.24	4.10	–	2.08	3.02	4.03	2.35	4.55	2.02, 2.19	1.41, 1.48
8	1680	1732	2.35	–	–	12.9	~2.45[r]	3.25	4.24	~2.45[r]	5.21	1.75, 2.20	1.53, 1.64
9	–	1714	–	–	–	~12.6	2.36	2.54[r]	3.76	2.52[r]	4.35	1.22, 2.05	1.26, 1.33
11	–	1732	–	1.21	4.10	~7.9	2.35	2.59	3.77	2.54	4.35	1.23, 2.07	1.27, 1.33

[a] In KBr discs (cm^{-1}). Further bands, νOH band: ~3345 (**9**), 3460 (**11**), νNH band: ~3230 (**2**), 3247 (**3**), 3318 (**5**), coalesced νOH (acidic & alcoholic) and or νN^+H_3 bands: 3250-2250 (**4**), 3600-3250 (**8**), 3500-2500 (**9, 11**), νC–O: 1014 (**2**), 1167 (**3**), 1108 (**4**), 1182 and 1047 (**5**), 1184 and 1060 (**7**), 1185 and 1155 (11);

[b] In $CDCl_3$ solution (D_2O for **4** and DMSO-d_6 for **8, 9** and **11**) at 500 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz;

[c] Assignments were supported by HMQC (except for **2**), for **5, 7, 9** and **11** by HMBC, and for **8** and **11** also by DIFFNOE measurements;

[d] Urethane group (**2, 3**), νC=N band (**7**);

[e] COOH (**1**, **4**, **8** and **9**), lactone (**2** and **3**), COOEt (**5, 7** and **11**);

[f] 3H (**5, 7** and **8**);

[g] Ethyl group, *J*: 7.1;

[h] Intensity 1H (**2**, **3**, **5** and **9**), 2H (**8**), coalesced signal of the acidic H's and the solvent (**4**), ~~or~~ the amide-NH and COOH (**8**), or the OH and NH_3^+ groups (11), , *d* (*J*: 6.5, **5**);

[i] ~ *t* (**2**, **4** and **7**), ~*s* (**9**) with coalesced lines, *t* (*J*: 4.7 for **3**), *d* (*J*: 4.5 for **11**);

[k] *dd*, *J*: 10.3 and 4.7 (**2-4**), ~ *dd* (**5**), *ddd* (**7**), *td* (**8**) with coalesced ines, *d, J*: 4.3 (**9**), 5.1 (**11**);

[l] Broad *m* (**2**), ~ *t* (**3**), ~ *d, J*: 9.3 (**4**), 4.3 (**9**), *dt*, *J*: 8.9 ad 3.5 (**5**), *m* (**7, 8** and **11**);

[m] Signals with coalesced lines, *m* (**2**, **5** and **8**),~*s* (**3**, **4** and **9**), ~ *t* (**7** and **11**);

[n] Broad *m* (1H) for **2** and **7-9**, *dd*, *J*: 5.6 and 2.9 (**5**), *m* (2H) for **3**, 2x*m* (2x1H) for **4**, *m* for **11**;

[o] *d* (1H), *J*: 5.0 (**2**), *m* (2H, **3**), *t* (1H), *J*: 6.3 (**4**), *dd* (1H), *J*: 5.6 and 3.0 (**5**), 2x*m* (2x1H, **7-9** and **11**),

[p] *AB*-type multiplet, 2x*d* (2x1H), *J*: 11.8 (**2** and **4**), 11.2 (**3**), 9.0 (**5**), 10.8 (**7** and **8**), ~ 10 (**9**), 11.5 (**11**), further split by long-range couplings of downfield / upfield *d* to *td* (**2** / **7**), both d's to *dd* (**9**) and downfield *d* to *m* (**7** and **8**), respectively;

[r] Overlapping signals;

Table 2. ^{13}C NMR chemical shifts[a] of compounds **2–5, 7–9** and **11** [b]

Com-pound	CH_3 [c]	CH_2	C_{quat} or CH_3 [d]	OC=O [e]	C=O [f] or C=N	C–1	C–2	C–3	C–4	C–5	C–6	CH_2(7)
						norbornane/ene moiety [g]						
2	28.7	–	81.0	176.6	155.8	51.4	41.8	54.6	48.2	24.5	89.6	35.6
3	28.7	–	80.4	178.1	155.9	47.8	43.4	54.1	40.7	32.5	81.1	35.6
4	–	–	–	179.9	–	48.4	42.1	53.9	39.7	31.1	83.1	35.3
5	14.5	60.9	23.8	173.8	170.1	47.6 [h]	47.7 [h]	52.5	47.4 [h]	134.3	137.6	48.0
7	14.7	60.3	21.9	172.2	156.6	34.5	50.1	50.3	36.8	73.4	33.2	37.9
8	–	–	19.9	172.0	171.1	34.7 [h]	48.9	46.1	36.9 [h]	79.3	32.6	36.1
9	–	–	–	174.8	–	42.7	51.3	54.7	43.3	72.6	40.2	35.2
11	14.9	61.5	–	173.5	–	42.8	51.2	54.8	43.3	72.5	40.1	35.2

[a] In ppm (δ_{TMS} = 0 ppm) at 125.7 MHz. Solvent: $CDCl_3$ (for **4** D_2O, for **8, 9** and **11** DMSO-d_6);
[b] Assignments were supported by DEPT, HMQC (except for **2**) and for **5**, **7**, **9** and **11** also by HMBC measurements;
[c] *t*-Butyl (**2**, **3**) or ethyl (**5**, **7** and **11**);
[d] Quaternary carbon (*t*-butyl, **2** and **3**), methyl (acetyl, **5** and **8** or oxazoline **7**);
[e] Lactone (**2**, **3**), carboxyl (**4**, **8** and **9**), ester (**5**, **7** and **11**);
[f] Carbamoyl (**2**, **3**), amide (**5**, **8**), C=N for **7**;
[g] For the numbering used in the Tables and in the spectroscopic part of the text, see **1** (Scheme 1);
[h] Interchangeable assignments.

Table 3. Physical and analytical data on compounds **1-11**

Compound	M.p.	Formula (Mw)	Calcd. /Found C (%)	H (%)	N (%)
1	183-187[a,b]	$C_{13}H_{19}NO_4$	61.64	7.56	5.53
		253.10	61.53	7.47	5.58
2	183-187[a]	$C_{13}H_{18}INO_4$	41.18	4.78	3.69
		379.20	41.23	4.87	3.58
3	145-150[c]	$C_{13}H_{19}NO_4$	61.64	7.56	5.53
		253.30	61.81	7.73	5.37
4	220-222[d]	$C_8H_{14}ClNO_3$	46.27	6.80	6.75
		207.70	46.38	6.97	6.69
5	64-67[e]	$C_{12}H_{17}NO_3$	64.55	7.67	6.27
		223.27	64.71	7.83	6.12
6a	Oil[f]	$C_{12}H_{16}INO_3$	41.28	4.62	4.01
		349.10	-	-	-
6b	Oil[f]	$C_{12}H_{17}BrNO_3$	47.70	5.34	4.64
		301.20	-	-	-
7	Oil	$C_{12}H_{17}NO_3$	64.55	7.67	6.27
		223.27	64.39	7.77	6.43
8	225-235[d,g]	$C_{10}H_{15}NO_4$	56.33	7.09	6.57
		213.24	56.49	7.21	6.42
9	240-245[h]	$C_8H_{14}ClNO_3$	46.22	6.74	6.74
		207.7	46.32	6.88	6.59
10	230-235[h,i]	$C_8H_{13}NO_3$	56.13	47.65	8.18
		171.20	-	-	-
11	210-211[h]	$C_{10}H_{18}ClNO_3$	50.96	7.70	5.94
		235.70	51.13	6.84	6.16

[a] iPr$_2$O;
[b] lit. m.p. 126-127 °C [27];
[c] iPr$_2$O-EtOAc;
[d] H_2O-acetone;
[e] n-hexane-iPr$_2$O;
[f] sensitive to the air; it was therefore used without purification in the next step
[g] with decomposition;
[h] EtOH-Et$_2$O;
[i] diastereomerically enriched (8:2) mixture